

## Comparison of the efficacy of intrauterine diclofenac and ibuprofen pellets as adjuvants to quinacrine nonsurgical female sterilization

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### Abstract

To investigate relative efficacy of intrauterine diclofenac and ibuprofen as adjuvants to intrauterine quinacrine for nonsurgical sterilization, a total of 900 women were systematically allocated to 2 monthly insertions of pellets of diclofenac (75 mg) or ibuprofen (55.5 mg) as adjuvants to intrauterine quinacrine (216 mg) in a rural private practice in West Bengal, India. All women were prescribed oral contraceptives for three months from first insertion. In the middle of the study increased care was taken to insert pellets at the fundus. There was no statistically significant difference found in cumulative life-table pregnancy failure rates at 36 months for women receiving diclofenac ( $2.7 \pm 0.82$ ) or ibuprofen ( $3.4 \pm 0.89$ ). Taking care to insert pellets at the fundus resulted in a decline of failures at 24 months from  $4.4 \pm 0.92$  to zero. Intrauterine administration of pellets of quinacrine (216 mg) plus diclofenac (75 mg) or ibuprofen (55.5 mg) with 3 months' oral contraception provides acceptable efficacy if pellets are inserted to the fundus.

### Introduction

The quinacrine pellet method of nonsurgical female sterilization as developed by Zipper and his colleagues [1] involves transcervical administration of 252 mg quinacrine hydrochloride as seven pellets through a modified Copper T intrauterine device (IUD) inserter. Two doses a month apart are given to nonpregnant women

during the proliferative phase of the menstrual cycle (days 5 to 12).

The drug causes occlusion of the fallopian tubes. Prehysterectomy studies of Merchant and her co-workers [2] show that the occlusion is due to inflammation and fibrosis (its extent depending upon the quinacrine dose) after a single insertion. She also noted that more closures were found by histopathology the longer the insertion to hysterectomy interval, leading to the recommendation of three months' contraception from first insertion.

Following the large field trial of the quinacrine pellet method of female sterilization in Vietnam [3] and based also on the experience of over 10 000 cases in West Bengal, India, the Indian Rural Medical Association has recommended this method for service programs in areas of high maternal mortality, of which West Bengal is one.

Zipper and his associates [4] investigated a lower dose of quinacrine (216 mg) in six pellets with the addition of an antiprostaglandin, diclofenac (50 mg), as intrauterine pellets and found an acceptable failure rate with two insertions. However, this trial was small and results inconclusive. Much larger clinical trials are needed to confirm this finding, and we wished to undertake such a trial in India. But diclofenac is very expensive in India, especially compared to the antiprostaglandin, ibuprofen. Through personal communications with Zipper regarding his experience with antiprostaglandins, we concluded that ibuprofen similarly administered should act in the same way as diclofenac. We decided to compare the efficacy of the quinacrine pellet method when these two antiprostaglandins are used as adjuvants. If these two antiprostaglandins are found to be comparable, then we want to undertake a much larger multicenter trial to determine if intrauterine ibuprofen improves the efficacy of the quinacrine pellet method.

### Materials and methods

The study was approved by the Ethics Committee of the Indian Rural Medical Association and conducted in the private chamber of one of its members (NRB). Women requesting a permanent method of contraception who were generally healthy and with at least three living children, the youngest being three or more years of age, were admitted to the study. Eligible women were asked to come to the clinic in the proliferative phase of their cycle where a physical and pelvic examination was performed. Systematically, every other subject was administered trans cervically, as described by Zipper [1], six pellets of quinacrine (216 mg) and three pellets of diclofenac (75 mg) or three pellets of ibuprofen (55.5 mg). The insertions were repeated a month later.

About halfway through the study, Hieu and his co-workers [3] analyzed their data which indicated great variation in failure rates among inserting clinicians. They hypothesized that this might be due to difference in insertion technique, that some clinicians failed to consistently insert the pellets at the fundus. The recommended insertion technique of Hieu [3] involves gentle insertion to the fundus, withdrawal of the inserter for one-half centimeter and advancing the plunger to release pellets at the

fundus. When the senior author was advised of this, he then took greater care to make all insertions of pellets to the fundus. To see the effects of this precaution, we divided the data set in two parts at approximately the date the senior author had been alerted.

The quinacrine pellets were custom manufactured (Sipharm, Switzerland); the release time for the quinacrine pellets was 30 min and for the diclofenac and ibuprofen 10 min. The modified Copper T inserter was cold sterilized and the pellets merely kept clean, as our experience and that of a large field trial in Vietnam [3] have shown this procedure does not increase risk of infection. Nine hundred women entered the trial between 10 September 1991 and 30 November 1993. All subjects were provided with three cycles of oral contraceptives to be started at the time of first insertion.

Systematic follow-up visits were not required, but the subjects and their families were well-known to the senior author, who practices in a rural area of West Bengal, India. To ensure that no pregnancy failures were missed, the women were offered a refund of the professional fee for the procedure (a large proportion of a family's monthly income) and a free first trimester abortion upon request for the pregnancy failures. Data were computer processed at the Indian Rural Medical Association offices in Calcutta.

### Results

Table 1 shows the life-table cumulative failure rates for each combination of medications. There is no statistically significant difference in failure rates between diclofenac (2.7 (0.82) and ibuprofen (3.4  $\pm$  0.89) as adjuvants to quinacrine at 36 months.

**Table 1. Cumulative life-table pregnancy failure rates per 100 women after trans cervical insertion of quinacrine (216 mg) with diclofenac (75 mg) ( $n = 450$ ) or ibuprofen (55.5 mg) ( $n = 450$ )**

Period (months)	Diclofenac		Ibuprofen	
	At risk	Cumulative failure rates	At risk	Cumulative failure rates
12	450	0.0	455	1.1
24	318	2.2	309	3.4
36	94	2.7	93	3.4
		SE		SE
		0.00		0.48
		0.76		0.89
		0.82		0.89

SE, standard error

Insertions: 10 September 1991 to 30 November 1993

**Table 2. Cumulative life-table pregnancy failure rates per 100 women after transcervical insertion of quinacrine (216 mg) with diclofenac (75 mg) or ibuprofen (55.5 mg) at two time periods of study: early (n = 500) and late (n = 400)**

Period (months)	Early insertions			Later insertions		
	At risk	Cumulative failure rates	SE	At risk	Cumulative failure rates	SE
12	495	1.0	0.44	400	0.0	0.00
24	481	4.4	0.92	146	0.0	0.00
36	187	4.6	0.94			

SE, standard error

Early insertions: 10 September 1991 to 17 October 1992

Later insertions: 19 October 1992 to 30 November 1993

The adoption of the Hieu insertion technique to ensure consistent placement of the pellets at the fundus resulted in a statistically significant decline in failure rate for the later insertions at 24 months ( $4.4 \pm 0.92$  vs zero). The result is shown in Table 2.

We had no serious complications in this series. Side-effects were similar to those reported by Hieu and colleagues [3], except that pruritis after insertions was rare in our experience.

## Discussion

We found no difference in the efficacy of the quinacrine pellet method between the diclofenac and ibuprofen groups. Thus, the effect on the efficacy of the quinacrine method of these two antiprostaglandins, if any, is the same. Zipper et al., because of the small number of subjects in their study, have not convincingly established that diclofenac improves the efficacy of the method. Larger studies than that published [4] are needed to confirm the effect of antiprostaglandins, if any, on efficacy. This study shows that ibuprofen can be used in place of diclofenac for this purpose.

Once the insertion technique was changed to ensure consistent placement of the pellets at the fundus, no further failure were observed. This finding offers further confirmation that Hieu et al. identified the major cause of failure of this method – inconsistent placement of the pellets at the fundus. Much emphasis should be placed on the importance of good training in the Hieu technique of insertion of the pellets.

The lack of systematic follow-up is the major shortcoming of this study. However, there are several good reasons to believe that few, if any, pregnancies were unrecorded. These women, all of whom tended to be very poor, had a significant economic incentive to return and report a pregnancy. Furthermore, the first author is

the only provider of abortion in the area. Since the treatment with diclofenac or ibuprofen was systematically assigned to every other case, the lack of systematic follow-up should not have affected one study group disproportionately in any case.

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## Resumé

Lors d'une étude conduite dans le cabinet médical d'une zone rurale au Bengale occidental (Inde) en vue de déterminer l'utilité relative du diclofenac et de l'ibuprofène en tant qu'adjuvants à la quinacrine, tous administrés par voie intra-utérine pour la stérilisation non chirurgicale, on a pratiqué sur un total de 900 femmes, à 1 mois d'intervalle, 2 insertions de pellets contenant soit 75 mg de diclofenac soit 55,5 mg d'ibuprofène en tant qu'adjuvants à 216 mg de quinacrine. Des contraceptifs oraux ont été prescrits à toutes les femmes pendant les trois mois qui ont suivi la première insertion. Au milieu de la période d'étude, on a veillé plus particulièrement à insérer les pellets au fond de la cavité. On n'a constaté aucune différence statistiquement significative dans les taux de succès sur les tables de survie cumulées à 36 mois, que les femmes aient reçu du diclofenac ( $2,7 \pm 0,82$ ) ou de l'ibuprofène ( $3,4 \pm 0,89$ ). En prenant soin d'insérer les pellets au fond de la cavité, il a été possible de ramener le taux de succès à  $4,4 \pm 0,92$  à zéro. L'administration par voie intra-utérine de pellets de 216 mg de quinacrine, plus 75 mg de diclofenac ou 55,5 mg d'ibuprofène, accompagnée d'une contraception orale pendant 3 mois est donc une méthode acceptable si les comprimés sont insérés au fond de la cavité.

## Resumen

A fin de investigar la eficacia relativa de diclofenac e ibuprofen intrauterinos como adyuvantes de la quinacrina uterina para la esterilización no quirúrgica, se asignó sistemáticamente un total de 900 mujeres a 2 inserciones mensuales de bolitas de 75 mg de diclofenac o de 55,5 mg de ibuprofen como adyuvantes de 216 mg de quinacrina intrauterina en un consultorio rural privado de Bengala Occidental, India. A todas las mujeres se les recetaron anticonceptivos orales durante tres meses desde la primera inserción. A mediados del estudio se prestó especial atención a la inserción de las bolitas en el fondo. No se determinó ninguna diferencia estadísticamente significativa en las tasas de fallo de las tablas de vida acumulativas a los 36 meses en el caso de las mujeres a las que se había recetado diclofenac ( $2,7 \pm 0,82$ ) o ibuprofen

(3,4 ± 0,89) El cuidado en la inserción de las bolitas en el fondo originó una disminución de los fallos a los 24 meses, de 4,4 ± 0,92 a cero. La administración intrauterina de bolitas de 216 mg de quinacrina más 75 mg de diclofenac o 55,5 mg de ibuprofén con 3 meses de anticonceptivos orales proporciona una eficacia aceptable si las bolitas se insertan en el fondo.