



A 22-year experience with quinacrine sterilization in a rural private clinic in Midnapore, India: a report on 5 protocols and 1838 cases

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Abstract

Objectives: Evaluate the safety and effectiveness of quinacrine for non-surgical female sterilization in five different protocols. **Methods:** The 5 trials were conducted sequentially. The first and largest, with 985 cases, tested the use of a curved inserter to place a 50 mg dose of quinacrine near each tubal ostia. The next 3 trials were carried out to determine the effect of adjunct procedures on the efficacy of the standard recommended protocol. The three adjuncts were 75 mg of intrauterine diclofenac, 10 mg medroxyprogesterone IM and either 10 mg of atropine IM or 20 mg of hyoscine butylbromide IM. The final trial focused on the currently recommended protocol. **Results:** The 100 mg dose placed at the tubal ostia with the curved inserter resulted in a failure rate of 9.0% at 20 years. Diclofenac or medroxyprogesterone did not improve efficacy over quinacrine alone. Atropine or hyoscine butylbromide substantially diminished the effectiveness of the quinacrine. The failure rate with the standard protocol in our series of 122 cases was 0.8% at 3.5 years. Side effects were minor. There were no deaths nor serious complications with any of these protocols. **Discussion:** All 5 protocols appeared to be safe and the standard one was the most effective.

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1. Introduction

After graduating from a homoeopathic medical college, I set up my office in 1980 in a mud hut at Maligram in the Midnapore District of West Bengal, India. My office was the only medical practice in the area which was not electrified until 1985. Government primary health centers were located at distances of 6 and 7 kilometers and a district hospital was 60 kilometers away. I was able to obtain additional training through courses provided by the Indian Rural Medical Association (IRMA), including the use of some allopathic drugs recommended by the World Health Organization for primary health care [1]. My practice grew rapidly and my clinic facilities improved into a brick building by 1990. It is housed presently in

a 3 storied 10 bed hospital, also used by some visiting qualified surgeons.

In 1981, I was selected by IRMA to participate in clinical trials of quinacrine sterilization. I was trained in the method by a qualified obstetrician/gynecologist at their headquarters in Kolkata (Calcutta). From May 1981 until March 1999, I participated in 5 clinical trials. IRMA designed the protocols and provided supplies. All trials were approved by the ethics committee of IRMA, known as the Executive Committee.

2. Methods and materials

The 5 studies are summarized in Table 1. I performed

Table 1
Summary of five quinacrine sterilization (QS) protocols conducted at Balichak, Midnapore, West Bengal, India, 31 May 1981 to March 1999 ($N = 1838$)

Name	Protocol Medications (mg)	Trials			
		pellets (N)	dose (mg)	insertions (N)	cases (N)
Curved inserter	Q 25	4	100	3	985
Diclofenac (D)	Q 36 with D 25	6 3	216 75	2 2	325
Medroxyprogesterone (M)	Q 36 with M 10 IM	6	216	2	313
Atropine (A)	Q 36 with A 10 IM	7	252	1	46
Buscopan (B) (hyoscine butylbromide)	Q 36 with B 20 mg IM	7	252	1	47
Standard	Q 36	7	252	2	122

all insertions. They were carried out in a uniform manner except for the curved inserter study. Using aseptic precautions as with an IUD insertion, a bimanual examination was made, a speculum introduced, a tenaculum applied and uterine depth measured. Clean pellets were loaded in a sterile, dry inserter and the inserter was gently passed through the cervical canal until it touched the uterine fundus. The device was then withdrawn 0.5 cm and its plunger slowly advanced to deposit all pellets at the very top of the fundus. The inserter and other instruments were then removed. The woman rested for 30 minutes in a supine trendelenburg position before discharge. All cases were prescribed 3 cycles of oral contraceptives at the time of the first insertion. Data were recorded on a register recommended by the International Federation for Family Health.

Materials received from IRMA were of foreign manufacture, except for the curved inserter trial for which quinacrine pellets were made to order by a pharmacist in Kolkata. The diclofenac pellets were produced in India. Life table rates were based on months of use from last insertion to most recent follow-up visit.

2.1. Curved inserter

The rationale for using the curved inserter was to place pellets as close to the ostia as possible. Half of the dose of 100 mg was loaded and inserted to one cornual angle, the device withdrawn, and the remaining pellets inserted to the other cornual angle. The 3 insertion protocol followed the procedure of

Zipper's original pellet study [2]. The protocol for this research was given up when a prehisterectomy study with comparative data showed no benefit of insertions at the cornual angles compared to the mid-fundus [3]. The study was initiated on 31 May 1981 and completed on 3 June 1991.

2.2. Diclofenac

The idea that diclofenac might both relieve pain associated with quinacrine insertions and possibly improve efficacy by relaxation of the tubal ostia was first suggested by Zipper and his colleagues [4]. This protocol included 2 insertions one month apart of 216 mg of quinacrine and 75 mg of diclofenac. After additional studies showed high efficacy without the addition of diclofenac or ibuprofen, they were deleted [5]. This trial was initiated 30 April 1991 and completed on 21 March 1994.

2.3. Medroxyprogesterone

Medroxyprogesterone is known to relieve uterine contraction. We thought it might also relieve spasm of the tubal ostia and thereby possibly improve the efficacy of QS by allowing more quinacrine to flow into the tubal lumens. Following earlier experience in the use of a method calling for quinacrine 216 mg to be inserted at 2 visits [4], we reasoned that medroxyprogesterone 10 mg IM be added to this protocol. The trial began on 28 February 1994 and was completed on 19 October 1996.

2.4. Atropine/Buscopan

Further thought on relaxation of smooth muscles to prevent spasm of the tubal ostia led to this comparative study (every other case assignment) of 2 smooth muscle relaxants, atropine 10 mg IM and Buscopan (hyoscine butylbromide, C.H. Boeringer Sohn, Ingelheim Am Rhein, Germany) 20 mg IM with 2 insertions of quinacrine 252 mg. This study began on 15 October 1996 and was completed on 29 October 1997.

2.5. Standard

When 2 insertions of 252 mg quinacrine were accepted as standard protocol [6], I adopted this procedure. Admissions began on 22 November 1997 and were halted on 9 March 1999, because the government banned the method following publication of an article in the *Wall Street Journal* attacking QS [7].

3. Results

Only minor complications and side effects were reported in the five studies. None required hospitalization and there were no deaths.

3.1. Curved inserter

Of 985 cases admitted, 39 were lost to follow-up. The life table cumulative failure rate was 7.4 per hundred women after 5 years and at 10 years it was 8.4. It increased accumulatively and only slightly to 9.0 at 20 years (Table 2).

Table 2
Cumulative life-table pregnancy failure rates for 3 insertions of 50 mg quinacrine to each cornual area using a curved inserter. Midnapore, West Bengal, India 1981–1991 ($N=946$)

Month	At risk	Rate (%)	Standard error (SE)
12	922	3.0	0.5
24	891	5.1	0.8
36	884	6.6	0.8
48	880	7.0	0.8
60	876	7.4	0.9
120	862	8.4	0.9
180	418	8.6	0.9
240	53	9.0	1.0

3.2. Diclofenac study

Of 325 cases admitted 11 were lost to follow-up. The life table failure rate at 10 years was 2.2 (Table 3). Diclofenac has been dismissed as an adjunct. The success in this series is owed to the quinacrine which was given twice in a dose of 216 mg.

Table 3
Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine (216 mg) and diclofenac (75 mg) at Midnapore, West Bengal, India. 30 April 1991 to 1 March 1994 ($N=314$)

Month	At risk	Rate (%)	Standard error (SE)
12	313	0.3	0.3
24	313	0.3	0.3
36	311	1.0	0.6
48	309	1.6	0.7
60	309	1.9	0.8
120	76	2.2	0.8

3.3. Medroxyprogesterone

Of the 313 cases admitted, 5 were lost to follow-up. The life table failure rate with this protocol was 2.9 after 7 years (Table 4). There were no failures after the third year.

Table 4
Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine 216 mg and intramuscular injection of medroxyprogesterone (10 mg) at Midnapore, West Bengal, India, 28 February 1994 to 19 October 1996 ($N=308$)

Month	At risk	Rate (%)	Standard error (SE)
12	304	1.6	0.7
24	300	2.6	0.9
36	299	2.9	1.0
48	299	2.9	1.0
60	299	2.9	1.0
72	238	2.9	1.0
84	121	2.9	1.0

3.4. Atropine/Buscopan

In this small comparative study 93 women were admitted, 46 for atropine and 47 for hyoscine butylbromide,

Table 5

Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine (252 mg) for sterilization when atropine or hyoscine butylbromide is administered IM at each insertion. Midnapore, West Bengal, India. 15 October 1996 to 29 October 1997 ($N=92$)

Month	Atropine 10 mg			Hyoscine butylbromide 20 mg		
	At risk	Rate (%)	Standard error (SE)	At risk	Rate (%)	Standard error (SE)
6	45	6.5	3.6	45	2.2	2.2
12	40	13.0	5.0	37	19.6	5.9
18	37	19.6	5.9	37	19.6	5.9
24	35	23.9	6.3	36	21.7	6.1

of which one was lost to follow-up. The 2-year life table failure rate among the women receiving atropine was 23.9% and among those receiving hyoscine butylbromide, the rate was 21.7%, both exceedingly high (Table 5).

3.5. Standard

In this trial of 122 women, the life table failure rate at 42 months was 0.8% (Table 6).

Table 6

Cumulative life-table pregnancy failure rates for 2 transcervical insertions of quinacrine (252 mg) for sterilization. Midnapore, West Bengal, India. 22 November 1997 to 9 March 1999 ($N=122$)

Month	At risk	Rate (%)	Standard error (SE)
6	122	0	
12	121	0	
18	121	0.8	0.8
24	121	0.8	0.8
30	121	0.8	0.8
36	118	0.8	0.8
42	57	0.8	0.8

4. Discussion

Because patients are not mobile, there is an advantage of a quinacrine trial in a remote private setting and that is the high rate of follow-up. All subjects were known to me as I have been their family physician for years. Also, conducting such investigations in remote rural areas offers a more realistic assessment of QS clinical

trials in these environments where this method can make the greatest difference to women's reproductive health care.

Perhaps the most important finding of our 22 years of experience with this method has been its excellent safety record. Women observe the outcomes of this procedure among their relatives, friends and neighbors. They discuss the results, often for years. Therefore there is no need to recruit women for QS. They learn about it from satisfied users and seek it on their own initiative. After 22 years, the women in my practice all know others who have undergone this procedure and they continue to come, in ever-increasing numbers asking for it. With their own observations in their own community, they have concluded that this method offers them the best alternative.

The only curved inserter pre hysterectomy study [3] involved small numbers. Considering the efficacy of this trial with such a low dose, a randomized comparative trial with pregnancy as an end point is still needed with a dose closer to an accepted standard. This might best be done initially with ultrasound control [8]. However, the increased skill needed for clinicians and the pain experienced by the patients might deter use of this protocol if improved efficacy is marginal over the present standard.

The failure rate in the diclofenac trial using 216 mg quinacrine for 2 insertions is most acceptable at 2.2% at 10 years. However, it is not significantly different from the standard protocol at 3 years (1.0% vs. 0.8%, respectively). This is also true of the medroxyprogesterone trial, where a failure rate of 2.9% after 7 years is excellent. However, comparing the two protocols, medroxyprogesterone vs. standard at 3 years, the difference (2.9 vs. 0.8) is statistically only

marginally significant; the rate of the standard protocol leans to be more favorable.

The failure rates of the two smooth muscle relaxants atropine and hyoscine butylbromide came as a surprise (23.9% vs. 21.7% at 2 years, respectively). Fortunately, this poor efficacy became evident early and this study was terminated. We can only speculate why these two drugs interfered with the action of quinacrine. The unexpected result may relate to the need for uterine contractions to advance dissolved quinacrine towards the ostia.

Use of the standard protocol of 252 mg quinacrine in our experience confirms the high efficacy and excellent safety of this method.

5. Conclusion

These trials have demonstrated that quinacrine sterilization can be safely and effectively delivered in a private rural setting in India. They have also shown that this method is very acceptable to women in remote areas. They continue to come in increasing numbers requesting this procedure despite the government's ban on using quinacrine for sterilization. The standard protocol like any protocol can be improved and we must continue to try new modalities to accomplish this. However, at this point QS remains the best and probably the only option on the horizon for many women and should be available to them now. I hope the

findings cited here will assist my government in making the decision to reverse the ban in India so that my patients can once again take advantage of this excellent alternative to surgical intervention.

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