ELSEVIER

Contraception

Contraception 64 (2001) 281-286
Original research article

Quinacrine non-surgical female sterilization in Bangladesh

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Abstract

This study was undertaken to evaluate the efficacy, safety, and acceptability of transcervical applications of quinacrine along with other adjuvants, such as ampicillin and ibuprofen, for sterilization. The cohort consisted of 750 normal women who requested sterilization and volunteered for this method at the family planning clinic of a tertiary hospital and community clinics in Chittagong, Bangladesh.

Several different protocols were followed from October 1989 to April 1999. Each woman received one or two insertions of 180 mg or 252 mg quinacrine with or without adjuvants including 55.5 mg ibuprofen or 125 mg ampicillin. Supplementary contraception was given in the form of combined oral contraceptive pills, barrier methods, or injection of depot medroxyprogesterone acetate for 3 months. Details of each protocol are described in the text.

The gross pregnancy failure rate for insertion of 180 mg in 590 women was 3.9% compared to 1.9% for the 160 who received 252 mg. There were no serious complications, and side effects were transient. We conclude that quinacrine non-surgical sterilization is a safe, acceptably effective method when two insertions of 252 mg quinacrine with medroxyprogesterone injection as a supplement is used.

Keywords: Quinacrine sterilization; Female sterilization; Quinacrine

1. Introduction

Bangladesh has a population of 120 million, growing by 2.2% annually, with a per capita income of less than US $310 [1]. Fertility has been declining because of an increased use of modern contraception, which has reached 50% of married women today. Nevertheless, about one third of pregnancies are reported as unplanned [2]. This is partly the consequence of irregular use of the oral pill, which accounts for 20.8% of contraceptive users. Female sterilization prevalence is 7.6% and has recently declined even further [2], no doubt due to lack of trained physicians and surgical facilities in predominantly rural areas of Bangladesh. A simple, non-surgical sterilization method is needed to fulfill unmet contraceptive demand.

In 1970, Zipper and his coworkers began to experiment with quinacrine and other drugs with scarring properties as an alternative to surgical sterilization. Among them, transcervical application of quinacrine pellets produced the best result [3]. Quinacrine was originally introduced in 1931 to prevent and cure malaria. Today, it continues to be prescribed for giardiasis and lupus erythematosus. This drug has sclerosant properties for some tissues and has been used for the management of recurrent pleural effusion. Controversy concerning its use for sterilization has been reviewed by Benagiano [4].

Quinacrine pellets for sterilization are introduced transcervically to the uterine fundus via a modified copper-T intrauterine device (IUD) inserter during the proliferative phase of the menstrual cycle. The procedure is similar to an IUD insertion and requires comparable technical skill. The pellets dissolve in uterine fluid within 30 min, and some flows into the proximal tubes. Quinacrine produces an aseptic inflammation and fibrosis of the intramural segment of fallopian tubes leading to occlusion of the lumen. Scarring requires 6-12 weeks [5]. Women are counseled to use a backup method of contraception for that period. We initiated use of quinacrine in our centers in Bangladesh to determine whether this method is an appropriate technology for our needs by assessing safety factors, efficacy, method acceptance, cost-effectiveness, and ease of delivery in a rural-based community.

2. Patients and methods

Clinical trials of quinacrine sterilization (QS) were started in October 1989. Initial encouraging results led to an

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0010-7824/01/$ - see front matter
PII: S0010-7824(01)00263-3

Table 1
Age distribution among 750 QS acceptors

Age (years)	Number	Percent
<25	19	2.5
26-30	182	24.3
31-40	460	61.3
>40	89	11.9

Table 3
Educational status among 750 QS acceptors

Level of education	Number	Percent
Illiterate	304	40.5
Primary	252	33.6
Secondary	141	18.8
Higher secondary	36	4.8
Graduation and above	17	2.3

expanded trial involving 750 women who requested sterilization and volunteered for this method. Trials were carried out in the family planning clinic of a tertiary hospital and in two community clinics in Chittagong, a major port city of Bangladesh. Participants were selected on the basis of national criteria for surgical sterilization, such as the woman's age being no less than 30 years and that she have no fewer than two living children, the youngest being at least 1 year old. Younger women of high parity were also accepted.

All the women were sexually active. They received quinacrine in the proliferative phase of the menstrual cycle (eighth to twelfth day) at least 6 weeks after termination of a pregnancy. Before admission to the study, the risks and benefits of the method and details of the procedure were carefully explained to those who chose this option. They then signed an informed consent form that acknowledged its permanent character as well as the candidate's preference for this method over others that were available.

The client's history was taken. She was then given a careful physical examination to rule out any uterine abnormality or pregnancy. Doctors trained in the copper-T IUD insertion technique carried out the procedure. Quinacrine pellets were introduced with a cold sterilized copper-T IUD inserter that had been air-dried after a spirit wash. The pellets were kept clean but not sterilized because quinacrine is known to be bactericidal, fungicidal, and antiviral [6]. A vaginal speculum was used to expose the cervix. The anterior lip was held with volsellum forceps. The utero-cervical length was measured with a uterine sound. The loaded inserter was gently introduced up to the uterine fundus. It was then withdrawn 5 mm and, while holding the outer sheath steady, the plunger was advanced to release all the pellets at the fundus.

Additional contraceptives, such as condom, combined oral contraceptive pill, or injection of depot medroxyprogesterone acetate (Depo Provera, Upjohn, Kalamazoo), were prescribed for 3 months after quinacrine insertion. A follow-up schedule at 3, 6, and 12 months and yearly intervals thereafter was established. The clients were asked to report accordingly and in-between if necessary.

In an attempt to increase the efficacy of QS, several different protocols were tried as follows:

1. Quinacrine (252 mg) for two insertions plus a combined oral contraceptive pill for 40 women, from October 22, 1989 to May 19, 1991.
2. Quinacrine (180 mg) plus ibuprofen (55.5 mg) for two insertions plus a combined oral contraceptive pill for 110 women, from May 20, 1991 to December 19, 1991.
3. Quinacrine (180 mg) plus ibuprofen (55.5 mg) plus ampicillin (125 mg) for two insertions plus a combined oral contraceptive pill for 215 women, from December 22, 1991 to December 8, 1993.
4. Quinacrine (180 mg) plus ibuprofen (55.5 mg) plus ampicillin (125 mg) for one insertion plus a combined oral contraceptive pill for 228 women, from January 1, 1994 to October 2, 1996.
5. Quinacrine (180 mg) plus ibuprofen (55.5 mg) plus ampicillin (125 mg) for two insertions plus injection of 150 mg Depo Provera [intramuscular (im)] for 37 women, from March 15, 1997 to April 9, 1997.
6. Quinacrine (252 mg) for two insertions plus injection of 150 mg Depo Provera (im) for 120 women, from April 9, 1997 to December 31, 1998.

Ibuprofen was used as an adjuvant when suggested by colleagues in Chile [7]. A small, randomized trial showed ampicillin to improve efficacy (B. Mullick, personal communication, 1991). The adjuvants such as ibuprofen and ampicillin were administered in an intrauterine fashion along with quinacrine.

Table 2
Distribution of 750 QS acceptors according to living children

Living children	Number	Percent
2	28	3.7
3	139	18.5
4	238	31.x
≥5	345	*46.0*

Table 4
Socioeconomic status of 750 QS acceptors

Income in US$ per month	Number	Percent
<20	136	18.2
20-40	218	28.9
41-60	188	25.1
>60	208	27.8

Table 5
Distribution of 750 QS acceptors by method of contraception before sterilization

Method used	Number	Percent
IUD	105	14.0
Pill	291	38.8
Condom	55	7.3
Injection	48	6.4
Safe period	22	2.9
Failed surgical sterilization	3	0.4
None	226	30.1

3. Results

Of the 750 women who volunteered for this procedure, **182 (24.3%)** were 26-30 years of age, 460 (61.3%) were **31-40** years old, and 89 (11.9%) were over 40. Only 19 (3.3%) of the women who received quinacrine were younger than 25 years (Table 1). Twenty-eight (3.7%) of them had two living children, 139 (18.5%) had three, and 583 (77.7%) had four or more (Table 2). Among quinacrine acceptors, 304 (40.6%) were illiterate. Of the remaining educated women, 17 (2.3%) were graduates of higher secondary schools or above (Table 3). QS acceptors were mainly lower income people (72.1%) who earned less than US $60 per month (Table 4).

Previous contraceptive users (524) accepted quinacrine more often than did non-users (226) (Table 5). Interval QS (70.3%) was more common than post menstrual regulation (26%) and postnatal cases (3.7%; Table 6). Women were lost to follow-up after quinacrine insertion in 396 (52.8%) cases, and the rest were followed through April 1999. The main side effects were lower abdominal pain (1.9%) and vaginal discharge (2.5%). These symptoms lasted a few hours to a few days. No changes in menstrual flow were reported by 95% of the women, 0.9% reported an increase in menstrual flow, 0.9% experienced spotting, and 3.2% of the cases were amenorrheic. Amenorrhea lasted not more than 6 months and required no treatment (Table 7). No uterine perforation, major complications, or deaths occurred in this study. There were 26 intrauterine pregnancies but no extrauterine ones (crude pregnancy failure = 3.4%). Pregnancy failures by protocol is shown in Table 8. Among all failure cases, conceptions in 21 cases were aborted by menstrual regulation. The rest of the pregnancies were carried to term. All these babies were examined at birth, and no malformations were noted.

Table 6
Time of insertion for 750 QS acceptors

Time	Number	Percent
After menstrual regulation	195	26.0
Interval	527	70.3
Postnatal	28	3.7

Table 7
Side effects/complications for 750 QS acceptors

Side effects/complications	Number	Percent
Menorrhagia	7	0.9
White vaginal discharge	19	2.5
Spotting	7	0.9
Secondary amenorrhea	24	3.2
Lower abdominal pain	14	1.9
Ectopic pregnancy	0	—
Fetal abnormality	0	—

Efficacy of quinacrine was not remarkably increased by decreasing the dose of quinacrine or with addition of adjuvants such as ibuprofen and ampicillin ($p > 0.5$; Tables 9 and 10). Pregnancy failure of quinacrine was not related to number of insertions, i.e., single versus twice in this series ($p > 0.5$; Table 11). Statistical analysis did not show any significant difference between use of additional contraceptives, such as combined oral pill, condom, or injectable contraception ($p > 0.1$; Table 12). Pregnancy failures occurred early after insertion and with the passage of time gradually declined (Fig. 1). Pregnancy failure for women younger than 35 years was higher than that for the women older than 35 (23 vs. 3).

4. Discussion

In daily life we are constantly required to make judgments based on a balance between the risks and benefits **of** our activities. This is especially true of medical decisions in both therapy and prevention. Risks and benefits change over time for various local situations. A developing nation such

Table 8
Pregnancy failure among 750 QS acceptors by protocol

Protocol Type		Failures	
	Number	Number	Percent
1. Quinacrine (252 mg) for 2 insertions + oral pill	40	1	2.5
2. Quinacrine (180 mg) + ibuprofen (55.5 mg) for 2 insertions + oral pill	110	3	2.7
3. Quinacrine (180 mg) + ibuprofen (55.5 mg) + ampicillin (125 mg) for 2 insertions + oral pill	215	11	5.1
4. Quinacrine (180 mg) + ibuprofen (55.5 mg) + ampicillin (125 mg) for 1 insertion + oral pill	228	9	3.9
5. Quinacrine (180 mg) + ibuprofen (55.5 mg) + ampicillin (125 mg) for 2 insertions + injection medroxyprogesterone (150 mg)	37	(–)	0
6. Quinacrine (252 mg) for 2 insertions + injection medroxyprogesterone (150 ma)	120	2	1.7

Table 9
Effect of dose of quinacrine pellets on efficacy of sterilization of 522 QS acceptors having two insertions*

	Doses of quinacrine					
	180 mg		252 mg		Total	
	#	%	#	%	#	%
Success	**567**	**96.1**	**157**	**98.8**	**724**	**96.7**
Failure	**23**	**3.9**	**3**	**1.3**	**26**	**3.3**
Total	**590**	100.0	**160**	**100.0**	**750**	**100.0**

* Chi-square with Yates correction = 0.90, p > 0.5 (NS).

as Bangladesh, with low contraceptive use, high population growth, and high maternal mortality, benefits greatly from increased contraceptive use. Risks and benefits of QS were analyzed in the form of safety, efficacy, acceptability, ease of delivery, and possibility of cancer and birth defects.

4.1. Safety

Maternal mortality in Bangladesh is 4 per 1000 live births, and each additional sterilization is estimated on average to prevent two births [2]. In this situation, each 1000 additional sterilizations using quinacrine would prevent eight maternal deaths. On the other hand, for an industrialized country with high contraceptive use, low population growth, and low maternal mortality, the benefits of QS are not as significant. The method is an outpatient procedure and does not need anesthesia, which, when used for surgical sterilization, can be associated with serious side effects and even death. Studies of such surgery in developing countries report rates of 50-100 deaths per 100,000 procedures [8]. In Bangladesh, 19 deaths per 100,000 surgical procedures have been documented [9], and in India it is 20 [10], compared to 3 in the United States [11]. There were no deaths in the present series, and no death has been reported for this method anywhere in the world [12]. Serious complications are also rare. Their reported rate with laparoscopic sterilization is 1.7% [13], so in a series of this size, 13 serious complications would be expected. Side effects were mainly lower abdominal pain, oligomenorrhea, amenorrhea, discharge, and pruritus vulvae. All were transient and of short duration, as found by others [5,14].

4.2. Efficacy

Zipper and his co-workers have reported a pregnancy failure rate of 3.1 per 100 women at 1 year, using three insertions of 252 mg quinacrine pellets [15]. Other investigators have observed that two or three insertions have given similar results [14,161. Our crude pregnancy failure rate was 3.4%. Hieu and his co-workers noted great variation in efficacy among inserting clinicians and hypothesized that this was due to different insertion techniques [5]. In the present series, insertion technique was uniform. The trial of Hieu et al. [5] showed improved efficacy by number of insertions, Our series shows only a moderate increase in failures for single compared to double insertion. Our failure to confirm efficacy reports of others may be due to our large lost-to-follow-up rate and to use of crude pregnancy rates, which is the main deficiency of the report since such rates do not distinguish between different durations of use. Most study participants attended the tertiary hospital that draws patients from a wide rural area. As they know menstrual regulation is free at the center, failures are more likely to return for follow-up, which would distort life table rates. Sokal and his co-workers [17] have documented improved efficacy for women 35 years of age or older. This is similar to the present study. Merchant's study also revealed an expected direct relationship between quinacrine dose and efficacy [18], which our data support; however, higher doses extend tubal damage beyond the intramural segment. Dr. Ljiljana Randic has shown that addition of ibuprofen to quinacrine does not improve efficacy [19]. In this series, the use of adjuvants along with low dose quinacrine (180 mg) did not improve the efficacy significantly (p > 0.5), and the data suggest ampicillin may increase failures. Failure rates of QS appeared to be higher in the early months of use. The pre-hysterectomy study of Merchant and her associates [18] shows that it takes 6 weeks for tubal closure to occur in a high proportion of cases. A randomized trial with and without an additional contraceptive has not yet been reported. A standardized protocol recommends 3 months of additional

Table 10
Effect of 125 mg ampicillin on efficacy of QS cases with two insertions of 180 mg quinacrine plus 55.5 mg ibuprofen

	With ampicillin		Without ampicillin		Total	
	#	%	#	%	#	%
Success	**231**	**95.5**	**107**	**97.3**	**238**	**96.0**
Failure	11	**4.5**	**3**	**2.1**	**14**	**4.0**
Total	**242**	100.0	110	100.0	**352**	**100.0**

Table 11
Number of insertions in relation to success of sterilization for 750 QS acceptors*

	Number of insertions					
	Single		Two		Total	
	#	%	#	%	#	%
Success	219	96.1	505	46.8	724	96.5
Failure	9	3.9	17	3.2	26	3.5
Total	228	100.0	522	100.0	750	100.0

* Chi-square = 0.20, p > 0.5 (NS).

contraceptive from first insertion [20]. In this series Depo Provera showed superior efficacy over oral pill and condom, hut not to a significant level. Our recommendation is for use of medroxyprogesterone because of its assured effectiveness for 3 months.

Failure of surgical sterilization is frequently due to fistula formation [21], which does not occur with the quinacrine method [18]. It appears that QS is an all or none response. If the drug reaches the tube, it nearly always results in closure, and most failures occur if it does not enter the tubal lumen. This could be because of tubal ostial spasm or a layer of endometrium covering the ostia. In this series, there was no report of ectopic pregnancy, a risk that is similar for surgical [22] and QS [5].

4.3. Acceptability

It is usual that a non-surgical method is more acceptable to women than one involving surgery. In Bangladesh, where both procedures have been performed in the same settings and despite government financial incentive to opt for the surgery, more than 750 QSs have been carried out.

4.4. Ease of delivery

The pellets and inserters cost less than 25 cents (US) per sterilization, which is affordable to the world's poorest women if it is made accessible. This procedure can be done by anyone trained in IUD insertions. Expansion of the services can be very rapid in a rural-based community with an inadequate doctor to population ratio because the method requires no anesthesia, surgery, or hospitalization.

4.5. Birth defects

There is limited human experience reported to date for accidental quinacrine insertion in pregnancy. For a birth defect to occur with this method would require insertion of quinacrine during early pregnancy, a teratologic effect of quinacrine, and the pregnancy to be carried to term. An estimate of the probability of these events occurring together [23] suggests the risk of a birth defect is very low.

4.6. Cancer

Cancer risk was not evaluated in this study, but long-term follow-up of cases in Chile shows no increased risk of cancer [24]. Long-term use of this drug for malaria suppression has revealed no increased risk of any malignancy [25].

5. Conclusion

The plight of poor women worldwide who are desperate to feed their children is such that they desire nothing more than safe and effective methods to curtail an addition to their family. QS would satisfy such an unmet need for those who have reached their desired family size. The failure rate of this method is somewhat higher than that of surgical sterilization, but it is much safer. Long-term evaluations to date confirm that it is not hazardous to health. QS is a safe, effective method when two insertions of 252 mg quinacrine with Depo Provera (150 mg) as 3 months of supplementary contraception is used. It should be an option for a well-informed woman.

Table 12
Effect of supplementary contraception on efficacy of quinacrine sterilization for 750 acceptors*

	Type of contraceptive					
	Oral pill + condom		Injection		Total	
	#	%	#	%	#	%
Success	569	96.0	155	98.7	724	96.5
Failure	24	4.0	2	1.3	26	3.5
Total	593	100.0	1.57	100.0	750	loo.0

* Chi-square with Yates correction = 2.04. p > 0.10 (NS).

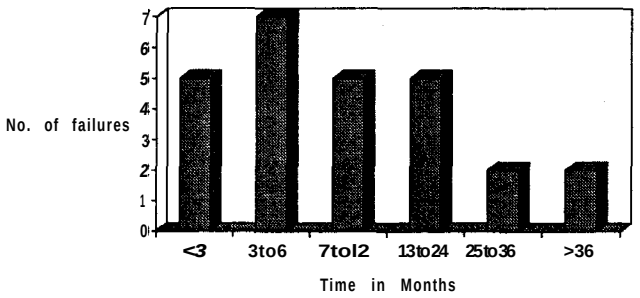

Fig. 1. Pregnancy failures over time among 750 QS acceptors.

Acknowledgments

Quinacrine and ibuprofen pellets were provided by the International Federation for Family Health.

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