EXTRA AMNIOTIC INJECTION OF ETHACRIDINE LACTATE (UNACREDIL) FOR TERMINATION OF PREGNANCY IN 2ND TRIMESTER

by

R. ANJANEYULU,* M.D., D.G.O.

S. P. DANI,** B.Sc. (Hons), M.D., D.G.O.

and

D. S. KAMAT,*** M.B.B.S.

Introduction

Of the number of methods advocated for termination of pregnancy in the 2nd trimester, the procedure of Intra-amniotic injection of hypertonic solution was well established and widely accepted. However, the commonly used solutions i.e. 20% saline and 50% glucose have many drawbacks. Glucose has the disadvantage of greater incidence of infection and occasional deaths have been reported after saline instillation due to inadvertent injection into the blood stream. The search for a safer solution led to the discovery of Rivanol or Acrinol lactate. Cohen in 1846 first described the extra-ovular injections for termination of pregnancy in second trimester. Kashiwara and Fujibayashi of Japan (1952) described the technique of injection of Rivanol by catheter in the extra-ovular space in 30 cases. Since then many Japanese workers have reported on Rivanol catheter technique with 90 to 100% success. Manabe from Japan (1969) studied in detail the mechanism of action of Rivanol and the effect of such extra ovular injection on circulating and urinary steroid levels and consequently on placental function. Lewis and Stillwell (1971) described the oxytocic effect of the acridine dyes and their use in termination of mid-trimester pregnancy Nabriski and Kalmanovitich (1971) modified the original Rivanol catheter technique by removing the catheter immediatley after Rivanol injection. However, the quantity of solution used was larger and their success rate was 94%. Carl-Axel-Ingemanson of Sweden (1973) compared the results of 'Rivanol' with extra-amniotic injection of hypertonic saline and concluded that the overall results with Rivanol were better and the initial success rate was 74% with saline induction as compared to 94% in Rivanol catheter group with remarkably few complications.

No reports have so far been published in India about results of Rivanol. The following is a study based on use of Ethacridine Lactate as extra-amniotic injection for termination of pregnancy in the 2nd trimester in 54 cases at the

Paper presented at Second International Seminar on Maternal & Perinatal Mortality, Pregnancy Termination and Sterilization held at Bombay on 3rd, 4th and 5th March 1975.

**Professor.*

***Reader.*

****Assistant Research Officer, I.C.M.R.*

Department of Obstetrics and Gynaecology, B.J. Medical College and Sassoon General Hospitals, Poona-1.

Accepted for publication on 27-10-75.

Sassoon General Hospitals and B.J. Medical College, Poona.

Material and Methods

Fifty-two healthy women and 2 patients, 1 with heart disease and 1 with severe hypertention and impending retinal detachment between 12-20 weeks of pregnancy, were subjected to M.T.P. by extra-amniotic injection of Ethacridine Lactate.

After disinfection of vagina, cervix was exposed by Sim's speculum and the anterior lip of cervix was held with Morrison's forceps. No dilatation was done. A sterilized Foley's catheter (No. 16) was introduced through the cervical canal by Magill's forceps. The catheter was inserted between uterine musculature and foetal sac for 15-20 cm. from the tip 0.1% solution of Ethacridine lactate was injected slowly by means of a syringe, 10 ml. per week of pregnancy to maximum upto 150 ml. The bulb was inflated with 5-10 cc of air. The outer end of the catheter was folded and tied with sterile gauze-strip. The catheter was kept in situ by vaginal tampon. To the apprehensive patients, Pethidine 50 mg. with siquil 10 mg. was given I.M. during the procedure. Patients were kept at complete bed rest for 4 hours, after which the tampon and the catheter were removed. If the patient failed to abort within 72 hours, reinstillation was done.

Unitocin (Spartine Sulphate) 150 mg. I.M. 1 hourly for 3 doses was given to assist the process of expulsion and evacuation done whenever considered necessary. No antibiotics were given prophylactically.

Observations

Age

Patients of all ages were included in this study. The youngest patient was 16 years old and the oldest 40 years.

Parity

Twenty-two of the 54 cases were unmarried. Two were primigravidae, one case of severe hypertension with impending retinal detachment and the other a case of illegitimate pregnancy.

Period of Pregnancy

Thirty-eight were between 13-16 weeks and 16 between 17-20 weeks of pregnancy. The mean gestation period was 15.96 weeks.

Injection Abortion interval

In 13-16 weeks group there were 38 patients. Of these 32 (84.2%) aborted after the first instillation of Ethacridine lactate. Injection abortion interval varied from 14 hours 50 minutes to 72 hours and 5 minutes with a mean abortion time of 35 hours and 39 minutes. The 6 cases that did not abort within 72 hours were given a second injection. All of them aborted within 48 hours, after the second instillation.

In the 17-20 weeks group there were 16 cases. Of these 12 (75%) aborted after the first instillation. The injection abortion interval varied from 15 hours to 72 hours 5 minutes, with a mean abortion time of 35 hours and 21 minutes. The four cases that did not respond to first instillation aborted within 48 hours after the second instillation.

Successful Termination of Pregnancy

In the 13-16 weeks group, 9 (23.6%) aborted within 24 hours, 27 (71.01%) within 48 hours and 32 (84.2%) within 72 hours. Even the 6 that did not respond with the first injection aborted after the second injection. In the 17-20 group, 4 (25%) aborted within 24 hours, 10

(62.5%) within 48 hours and 12 (75%) within 72 hours. The remaining 4 aborted after the second instillation.

The average successful rate within 72 hours was 81.4% and all the patients aborted after the 2nd injection giving an overall success rate of 100%.

In 50 out of 54 cases the abortion was complete. The foetus and the placenta were expelled intact. There was minimal pain and discomfort. The abortion resembled that of incompetent cervix. Unitocin 150 mg. (Spartin Sulphate) I.M. every hour for 3 doses were given in 3 cases to hasten the process. Digital removal of the placenta was done in these three cases and Surgical evacuation was done in one case. No case of cervical tear was seen in the above series. Postabortal bleeding was normal in 50 cases (92.8%). In only four cases it was slightly more and it responded to methergin tablets. No fall in blood pressure was noted either during or following abortion. Few patients had one or two vomitings but all those patients also required Pethidine as they were very apprehensive. None of the patients had a rise of temperature either during or after abortion.

Follow Up

Thirty-eight patients came for follow up one week after of abortion. Six complained of slight bleeding. In 2 the bleeding did not stop. On examination the uterus was firm and involuting and os was closed. The patients responded to oral contraceptive tablets. Twenty-five (46.3%) came for follow up after one month and none of them had any symptoms.

Discussion

When first introduced, Rivanol solution was used in the concentration of 1 in 2000. It was thought that this solution, in addition to its bactericidal effect, also increased the tonus of uterine contraction, Manabe (1969) reviewed the work of various Japanese authors. They advocated 50 ml. of solution to be injected through a sterilized Nelaton catheter (No. 12). The catheter was left in the uterus till complete abortion occured. Nabriski and Kalmanovitich (1971) advocated dose of 150 ml. for each lunar month of pregnancy. Volume of Rivanol injected varied from 500-700. The underlying principle was to separate the ovum from the uterine wall. Sweedish workers advocated a dose of 10 ml. per week of pregnancy to a maximum of 150 ml. In the present study the same dose schedule was followed but the catheter was removed after 4 hours.

Manabe (1962) suggested that Extra-ovular injection of Rivanol causes mechanical stimulation of the uterus. Extensive detachment of the membranes and the stimulation of the uterus caused by Rivanol in extra-ovular space can precipitate labour. The catheter left in situ also was thought to stimulate the uterine contractions. Mechanical stimulation can also cause reflex release of oxytocin.

Oxytocic action of acridine derivatives has been demonstrated in cats. Perfusion experiments during human uterine muscle strips have shown that there is an increase in spontaneous muscle contractility caused by a rise in resting tension and increased frequency and duration of contraction. In many cases the main component of the increase in the uterine contractility was rise in resting tension, which progresses to a tetanic contraction.

Disruption of placental function is not the cause of rise in uterine contractility. Manabe (1969) reported that urinary steroid levels and the plasma progesterone

levels do not drop significantly during the course of treatment. Also, histologically the placenta delivered by this method was normal except for slight superficial infiltration of polymorphonuclear leucocytes. The histological study of placenta in the present study showed no remarkable placental pathology and the only changes noticable in most of the placentae were in the form of areas of necrosis involving the maternal aspect of placenta, namely decidua compacta where the decidual structure was completely lost with infiltration of polymorphs and some degenerative changes. The chorionic villi (foetal part of the placenta) were healthy and did not show any pathological changes. Intervillous fibrin deposits were within normal limit. Some haemorrhages were occasionally visible.

Gustavi (1973) suggested that extra-ovular procedures (including injection of Rivanol) act by releasing lysosomal hydrolytic enzymes within decidual cells. The enzymes released are thought to cleave prostaglandin precursor from membrane phospholypids and thereby provide substrate for prostaglandin synthesis. It seems probable that the observed damage to decidual lysosomes is followed by the synthesis and release of prostaglandins resulting in uterine contractions and finally in abortion.

Comparison of Results

Inspite of different dosage schedules, it is seen from the Table 1 that the procedure has a high percentage of success. In the Rivanol cathetor method it was usually thought that the cathetor plays a great role in initiation of uterine contractions. Nebriski and Kalmanovitich injected large quantities so as to separate ovum and membranes from the uterine walls. In the present series the cathetor was kept only for 4 hours, and no supplementary oxytocic drip was given. Unitocin (Spartine Sulphate) was given only to complete the process of abortion. Even so, 44 out of 54 patients (81.4%)

TABLE I
Comparison of Results

	Author	Cases	Method	Dose	Time for removing catheter	Success rate
1.	Kabayashi (1957)	82	Rivanol + catheter	Rivanol 50 ml	Till abortion occurred	100% in 114 hours
2.	Nabriski and Kalmanovitich (1971)	52	Rivanol	Rivanol 150 ml/ Lunar monh	10 minutes after instillation. Oxytocin drip in 90% cases	93% in 24 hours
3.	Carl-Axel Ingemanson (1973)	53	Rivanol + catheter	Rivanol 10 ml/ week max. upto 150 ml.	Till abortion occurred	94% in 72 hours
4.	Present study (1975)	53	Unacredil	Ethacridine lactate 10 ml/week max. 150 ml.	4 hours after instillation	81.4% in 72 hours 100% after reinstillation

aborted within 72 hours after first instillation. The rest of 10 patients also aborted after the second instillation giving a 100% success rate without resorting to any other method.

Advantages of the Procedure

Ethacridine lactate or Rivanol has a wide margin of safety . The minimum lethal dose is 50 mg. per kg. In animals and human beings intravenous injection had no adverse effect, when given in dilution of 0.1% so that there is no danger of intravasation when injected into extra-amniotic space.

Its potent and wide spread bactericidal properties minimised the danger of per vaginal infection after extra-ovular injection. In none of the patients treated was there any infection during or after the abortion.

The technique itself is simple. It does not need any complicated set of instruments. No dilatation of cervix is required. Even in unmarried patients there was no difficulty in passing the catheter. Very few patients complained of slight discomfort during insertion of catheter.

The chances of placental damage from inadvertent rupture of membranes is inconceivable because of the soft nature of catheter in contrast to a solid bougie.

The method can also be used in patients whose cardiac and kidney functions are impaired. In the present study it was used safely in one case of hypertension with impending retinal detachment and in one case of heart disease without any complications.

There are many who believe that there are no special contraindications for this procedure when used in the late mid-trimester cases. Manabe observed that the foetus usually delivered alive, which indicates that Ethacridine lactate produces far more physiological labour unlike hypertonic solutions.

One remarkable observation in present series was that none of the patients complained of pain. Twenty-six patients had slight discomfort in the abdomen accompanied by minimal bleeding. The abortion process was sudden and in 50 cases was complete. It resembled the abortion in cases of incompetent cervix. The foetus was expelled with intact sac and placenta.

Complications

If used in high concentrations such as 1-2% Ethacridine causes anuria. The concentration for extra-ovular injection should not exceed 0.1%.

No long term effect on the uterine decidua was observed in the reported series. There was no possible effect of leakage of the solution in the peritoneal cavity.

It is established that this technique of extra amniotic injection of ethacridine lactate is simple, safe physiologically effective and without any complications.

Acknowledgement

Our thanks are due to the Dean, B. J. Medical College and Sassoon General Hospitals, Poona-1 for permitting us to undertake this clinical trial and publish this paper.

Our grateful thanks are to Shri Amrut Mody, Managing Director, Unichem Laboratories, Ltd., Bombay for going out of the way to manufacture this drug and for giving it to us for this clinical trial.

We are also thankful to the Director of Medical Education and Research, Government of Maharashtra and also the Director of Health Services, Government of Maharashtra, Bombay for helping us in getting this drug.

References

1. Carl-Axel. Ingemanson. Am. J. Obst. & Gynec., 115: 211, 1973.
2. Gustavi, B.: Am. J. Obst. & Gynec., 120: 531, 1974.
3. Lewis, B. and Stillwell, J.: J. Obst. & Gynec. Brit. Comm., 178: 838, 1971.
4. Manabe, Y.: Am. J. Obst. & Gynec., 105: 132, 1969(a).
5. Manabe, Y.: Am. J. Obst. & Gynec., 103: 232, 1969(b).
6. Manabe, Y.: Obst. & Gynec. Survey, 27: 701, 1972.
7. Nabriski and Kalmanovitich: Am. J. Obst. & Gynec., 110: 54, 1971.