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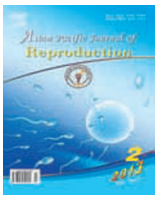

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# RISUG: A new perspective in non-hormonal male contraception

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ABSTRACT

Currently there are several hormonal and non-hormonal methods of contraception available but due to long term side effects of hormonal contraceptives, a great research is undergoing to develop an effective and noninvasive non- hormonal male contraceptive. One of the product of this research is RISUG (an acronym for the Reversible Inhibition of Sperm Under Guidance). RISUG is a co-polymer of Styrene Maleic Anhydride (SMA) dissolved in Dimethyl Sulfoxide (DMSO) to form a gel. This gel is then introduced in the lumen of male vas deferens which results in the partial blockage of vas deferens. It causes the disruption of the membrane of spermatozoa and release of enzymes that are essential for the fertilization of ova. Thus the ejaculation after RISUG contains infertile spermatozoa.

## 1. Introduction

Today the huge growth of world population is one of the biggest challenges faced by the human race. In 1997 the world population was 5.8 billion and currently it is around 7 billion and it is expected that it will be 8 billion by 2025, 9.1 billion in 2050 and 19 billion by the end of twenty first century[1,2]. As the global population continuously increasing very sharply, there is an urgent need to increase the choice of effective contraception methods. Indeed today we have both hormonal and non-hormonal methods available for the male contraception. However the long term use of hormonal contraceptives (androgen, progestin) might associate with serious adverse reactions such as cancer, obesity, hypertension and blood clotting. Thus the non-hormonal contraceptives might be more suitable than hormonal contraceptives because they do not affect the functioning of male sex organs such as prostate gland. Currently many non-hormonal male contraceptives are under various stages of research and development[3].

## 2. Reversible inhibition of sperm under guidance

RISUG (Reversible Inhibition of Sperm Under Guidance), is an injectable compound which has completed its phase I and II clinical trial and now under phase III clinical trial in India[4,5]. It consists of a co-polymer of Styrene Maleic Anhydride (SMA) dissolved in Dimethyl Sulfoxide (DMSO) to form a gel. This compound is injected into the lumen of vas deferens by no scalpel technique and provides contraception for at least 8 to 10 years[6].

## 3. Mechanism of action

RISUG is a poly electrolytic compound. It is introduced in the lumen of vas deferens, where it comes in contact with the spermatozoa[7]. On contact with the spermatozoa, due to its poly-electrolytic nature, it cause ionic imbalance on the human sperm membrane which results in swelling and rupture of the sperm head (Acrosome) and leakage

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of enzymes (Hyaluronidase and Acrosin) necessary for the fertilization of ova[8]. RISUG results in partial blockage of vas deferens associated with the flow of functionally inactive cells[9]. The RISUG ejaculates consist of partially or completely damaged spermatozoa which functionally become unable to fertilize the ova. The earlier studies carried over langur monkeys have shown that vas deferens with SMA results in severe oligospermia or azoospermia in first two ejaculations and continuous azoospermia in subsequent ejaculations[10]. Release of enzymes necessary for fertilization is discussed in Figure 1.

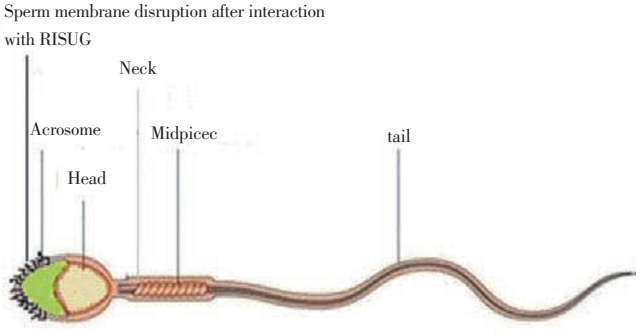


**Figure 1.** Membrane disruption and release of enzymes which are necessary for fertilization.

## 4. RISUG administration

The RISUG is administered into the vasa deferens by using a non-scalpel method and requires only 15 minutes to complete the procedure. Once the RISUG administered into the lumen of vas deferens, it fixed firmly to very small folds on the inner surface of vas deferens with in 72 hour of injection[11]. In first clinical trial of RISUG, it is found that the therapeutic dose of the drug is 60 milligram[12]. The persons who had administered the drug in second clinical trial have now been using the drug for more than 10 or 15 year without any problem. After the proper implantation of the drug, there is no pregnancy found to occur during the 1-3 year of the clinical study[4]. RISUG injection into vas deferens has been described diagrammatically in Figure 2.

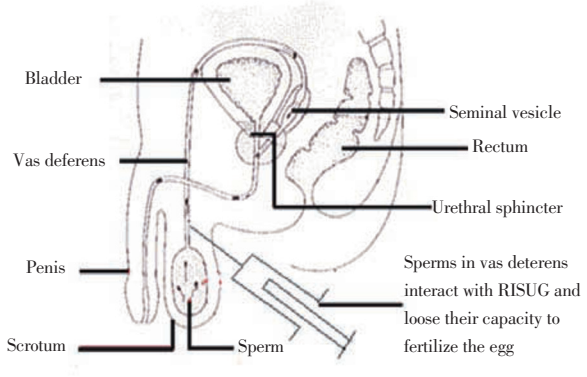


**Figure 2.** RISUG injection into vas deferens.

## 5. RISUG reversal

Earlier studies in primates have shown that RISUG is easily reversible. The studies have been shown that multiple injections and reversal is effective in primates[13]. The noninvasive reversal of RESUG is obtained by flushing it out from the lumen of vas deferens by dissolving in an appropriate solvent[14]. It can also be removed by stimulating the vas deferens percutaneously[15]. In one of study it is reported that an injection of baking soda dissolved in water flush out the drug from the vas deferens effectively[14]. Another study showed the effective removal of the RISUG from the lumen by massage, vibration and low electrical current[16]. The study on primates put forward that it would take some months for the whole reversal of RISUG's contraceptive effects[17]. Unlike vasectomy, RISUG does not cause any kind of auto-immune response and its reversal is very much trustworthy[18].

## 6. Other reported activity

In addition to contraception, RISUG has also shown to possess antimicrobial activity. The research has proven that RISUG possesses potent antimicrobial activity against a number of microorganisms such as *Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and *Neisseria gonococci*[20]. The viruses are more susceptible to its antimicrobial action than the vegetative form of bacteria such as *Staphylococcus* and *Pseudomonas*. The drug has shown to possess anti-HIV activity due to its electrical charge effect [19,20].

## 7. Future prospective

RISUG is a polymeric complex of SMA and DMSO[8,21]. On its administration into the lumen of vas deferens, it reacts with the water molecule, lipids and proteins present in the spermatic fluid resulting in gel formation. Progressively the SMA gets converted into styrene maleic acid and mandelic acid. The mandelic acid and styrene maleic acid (SMAac) which are released from the RISUG implant gradually moves with the spermatic fluid along the vas deferens to the ejaculatory duct and to the semen. The SMA and mandelic acid mix with the spermatic fluid and deactivate the HIV present in the semen[20]. The anti-HIV activity of mandelic acid has been already proven[21]. Thus it helps to clear the semen from HIV virus. Another proposed additional

action is through hyaluronidase, released during the acrosome reaction. An increase in the number of acrosome reacted sperms result in increase in the concentration of hyaluronidase enzyme in spermatic fluid. Hyaluronidase acts over tissue collagen protein and facilitates the entry of HIV virus into tissue[20,22]. Hyaluronidase increases the penetration of HIV virus into the tissues thus HIV absorbs in to the surrounding tissue from the seminal fluid. Ultimately the seminal HIV load will further reduce and the whole semen will be free from the HIV. The foremost problem of antiretroviral therapy is that most of the host body reservoir are resistant to the entry of anti-HIV drugs. The hyaluronidase will increase the absorption of virus into the nearby tissue and not to the structures from which the virus is instigated. Now the tissue containing the virus is likely to be less protected to the action of anti-HIV drugs and results in the greater exposure of the virus to the drug at low dose and thereby produces lesser side effects[20].

## 8. RISUG: as an entry inhibitor for HIV

Entry inhibitors are the type of antiretroviral drug that inhibit the entry of HIV into the host immune cells. A hypothesis is set forward in which a new non-hormonal male contraceptive, RISUG with confirmed antimicrobial activity is recommended as a potential entrant for entry inhibitor group of antiretroviral drugs. The suggested mechanism of action of RISUG includes (1) it interacts with the gp120 (a viral surface protein) and thus prevents the binding of the virus to the cell surface of CD4 helper T cells and (2) competitively binds with viral surface glycoprotein and thus prevents the glycoprotein-cell surface glycosaminoglycan Heparan Sulfate(HS)[23]. Possible mechanism of action of RISUG as an entry inhibitor, anti-retroviral drug is given in Figure 3.

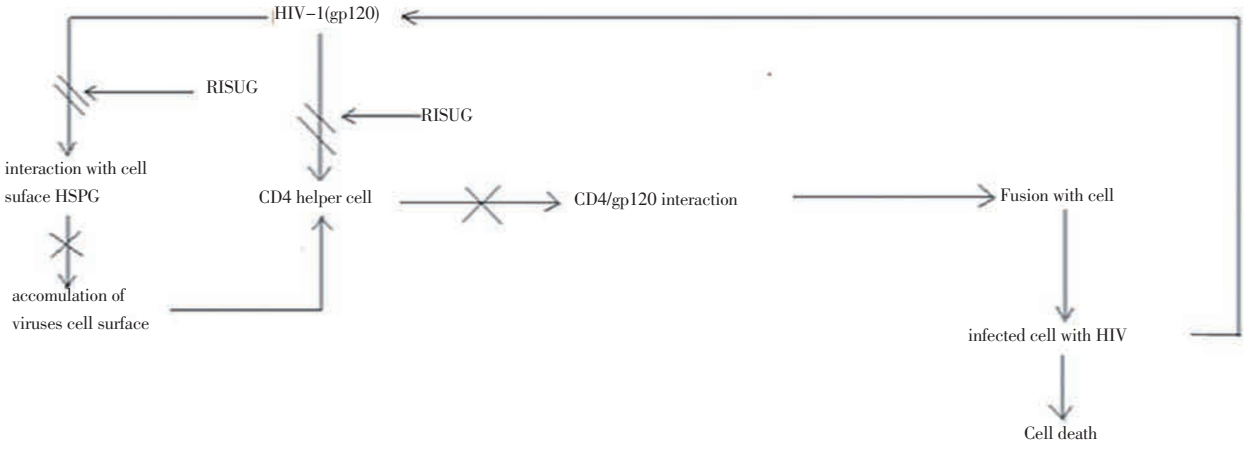


**Figure 3.** Possible mechanism of action of RISUG as an entry inhibitor, anti-retroviral drug.

## 9. Expected side effects of RISUG

In phase II clinical trial some participants showed minor swelling of testes with no concomitant pain. The swelling resolved within 2 weeks after injection of RISUG without any treatment[24]. Unlike vasectomy RISUG does not show autoimmune response and granulomas[18]. Another fear accompanying vas deferens occlusion is declined prostate gland health. But men from phase II clinical trial 8 years after receiving the RISUG had healthy prostate[25].

## 10. Conclusions

Today the RISUG is under extensive research and development and in clinical phase III trial in India. The conventional hormonal contraceptives produce numerous side effects on their long term use. The non-hormonal male contraceptive RISUG provides effective contraception without producing any type of serious adverse reactions. In addition to contraceptive activity it is proposed that the drug may be having anti-HIV activity. Thus RISUG might be a potential non-hormonal contraceptive in upcoming years.

## Conflict of interest statement

We declare that we have no conflict of interest statement.

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