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Modern Aspects of Suppositories: A Review

Aman Kumar, Arindam Kolay, and Ujwal Havelikar

ABSTRACT

Suppositories are an underutilized dosage form. Suppositories are such types of dosage forms used to provide medication via the vaginal and rectal routes. Vaginal suppositories are commonly referred to as pessaries. It was developed from a formulation called Liquid Enema. Enema has a great disadvantage in that, it used to leak out of the cavity in which they were put. So, this led to the discovery of suppositories as an alternative method of medication. Suppositories can be described as semi-solid dose forms utilized to provide medications for therapeutic action via rectal, vaginal, or urethral routes, where they will melt or dissolve and deliver localized or systemic impact. It is composed of cocoa butter, PEG, and fatty base (and a few others) as main ingredients, and it comes in different shapes and sizes.

Although suppositories were formulated it was not that stable inside the orifices and also used to draw out of it. So, in order to overcome the problem of leaking, researchers added some mucoadhesive substance to improve its stability. From here onward improvement in the suppositories started as an alternative medication other than oral dosage form. The current article aimed to fabricate descriptive information about the advancement of suppositories. These advancements are Bi-layered Suppositories, Homogeneous Plain Suppositories, Hollow Suppositories, Effervescent Suppositories, Gel suppositories, Sustained Release Suppositories, etc.

Keywords: Advancement in suppositories, Composition, Formulation, Modern Concept, Suppositories.

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I. Introduction

Suppositories are an underutilized dosage form [1]. Suppositories are a type of dosage form used to provide medication via the vaginal and rectal routes. They developed from liquid enema formulations as a more practical alternative method of medication administration. Before the discovery of suppositories, this enema had a great disadvantage that it used to leak out of the cavity in which they were put in. The name "suppositorium" derives from the Latin word supponere, which means "substitute" [2]. Suppositories can also be administered vaginally. It is commonly referred to as pessaries. The word Pessaries was derived from Greek word “pessarium”, which means pesos, meaning "oval stone" [2]. However, work has already begun in recent years, particularly in Europe and a few American research institutes. Meanwhile, nations like the UK and the USA have not been utilizing suppositories or experiencing antipathy against them, especially for rectal medicine delivery. While eastern Europe's continent, notably France and Italy, has the highest acceptability [1].

A. Definition

A suppository is defined in a fairly vague manner. Only the EP contains a separate chapter on rectal dosage forms among the USP, European, and Japanese Pharmacopoeias (USP, EP, and JP, respectively). A suppository is solely defined by the USP and JP as a dosage form designed for rectal administration. In order to deliver a local or systemic impact, suppositories are described as an administration method that is administered into the rectum or vagina [3]. Depending on the point of reference, suppositories can be described in numerous ways. Functionally, they are best described as semi-solid dose forms utilized to provide medications for therapeutic action via rectal, vaginal, or urethral routes. They melt in the body temperature and then dissolved to give systemic and localized action and serve as an alternative to oral route of administration [4].

B. Compositions

They typically comprise of a stiff or semi-rigid base, an inert matrix, and the active ingredient. The active and inactive components do not interact chemically during this dispersion. This is done to prevent change from either the active substance or the suppositories themselves. The dispersed phase can be added to suppositories as a liquid or a solid (powder) (either aqueous, alcoholic, glycolic solution or it can be oil and extracts). Based on their capacity to melt or dissolve at body temperature, the materials for bases can be acquired either naturally or artificially. There are different bases available, and these are being used according to the requirement of the formulations. These may be either Fatty base, PEG or Supposiblends etc. [2], [3].

C. Shapes and Sizes

The finished suppositories are created in various shapes and sizes in order to deliver the optimum therapy as per necessity, such as, type of active component, route of

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administration, age and condition of the patient, desired release pattern etc. [5]. They are also accessible in a variety of physical forms; they can be compressed or moulded, covered in foil or plastic, or enclosed in gelatine. The most popular suppositories come in the following sizes:

- **1 g:** it can be either bullet-shaped or cone-shaped and has a rounded apex [1], [5].
- **2 g:** the 2 g size is torpedo-shaped but has the same shape as the 1 g size. Their bottom or later half is progressively widening for around three-quarters of their length while maintaining a blunt or pointed peak. As a result of its broadest portion, there is a benefit: after insertion, the anal sphincter muscles push the suppository into the rectum [1], [5]. The most typical commercial product size is 2 g. The size of a glycerol suppository for an adult is 4 g. It can also be cone-shaped with a rounded tip and weighs 4 g or 8 g.

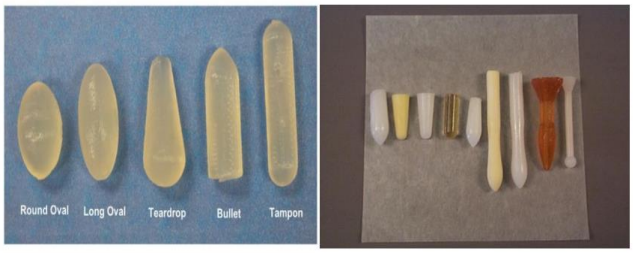

Fig. 1. Showing different shapes and sizes of suppositories.

D. Ideal Properties of Suppositories

Following should be the properties of suppositories:

It should melt at body temperature or dissolve, or it should be dispersed in the body fluids. It should release there medicaments radially. It should be compatible with any medicament when added. Most importantly it should be non-toxic and non-irritant to the mucous membrane. It should not interfere in release or absorbance of drug. It should be stable on storage. It should not be softened or hardened on storage. It must retain their shape and size. It should have kept their shape intact when handled. It should be stable when heated above its melting point. Also, it should not adhere to the surface of the mould and also it should shrink sufficiently while removing from the mould [1].

II. Applications

Traditionally suppositories were chosen to use for local usage or in that case where other routes of administration were unavailable; a wide range of drugs have been added into this dosage form.

Now a days, it has its application as local anesthetic's, laxatives, local antibiotic treatment. Suppositories are increasingly important for systemic delivery. Form the past few years, suppositories are very much being sold for their application as anti-inflammatory, analgesics, antipyretic, and sedative and hypnotics. They contain local anesthetics such as cinchocaine and benzocaine. The drug like aminophylline helps in relaxing the involuntary muscle especially for asthmatics and chronic bronchitis, morphine is also used as analgesic.

From the future point of view, there are many on-going work or research are already being directed on various authorized labs or at research centre in all over the world. Recently they have been working on INSULINE THERAPY in suppository form and also for ANTI-HIV and the result is coming out to be promising. Hope for better outcomes in the coming years.

A. Advantages

Suppositories do offer a number of advantages.

The most important advantages are that it avoids first pass effect/first pass metabolism and hence gives its localized effect through the systemic circulation. Suppositories are such that it should melt at body temperature, as a result it produces therapeutic systemic effect. It also has one of the great advantages in administrating the medication to the unconscious patient. It is easy to use for paediatrics and geriatric patients. In the case of children, it has always been a tougher task to medicate them so in that case theses suppositories can be used. Useful in rapid and direct effect in rectum since it gives local effect. These are also used in the case of constipation as it is helpful in the evacuation of bowel. Convenient for those drugs causes GIT irritation, vomiting etc. by avoiding the hepatic first pass elimination it enhances the drug bioavailability. It can also be administrated to the old or the mentally disturbed patient via rectal route [1], [2].

III. Mechanism of Action

A suppository will first dissolve in the liquid or melt on the mucous layer depending on whether it is hydrophilic or lipophilic. The osmotic properties of the dissolving vehicle cause water to be drawn to the rectum or vagina, and when the suppository melts and dissolves, the drugs it contains will diffuse out toward the mucosal epithelial surfaces. If the drug is water immiscible, it must first break free from the base of the suppository by the action of gravity or ambulation before it may begin to dissolve in liquid. The softening and dispersion of lipophilic melting suppositories are not dependent on the presence of fluid. The same method of medication administration is used in suppositories, which dissolve when heated [6].

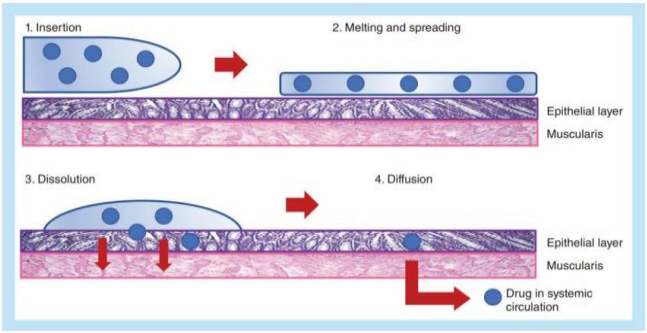

Fig. 2. Showing Mechanism of Action.

IV. Main Classes of Suppository Base

A. Cocoa Butter

Theobroma oil is another name for it. By compressing the seed oil or using a solvent, cocoa butter may be made from

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Theobroma cocoa seeds (chocolate beans). Saturated and unsaturated fatty acid triglycerides are present in cocoa butter. It is a yellow material that is solid at normal temperature but melts at body temperature. It has a distinct, strong odour. Due to the absence of emulsifiers in cocoa butter, it does not absorb any water. The ability of cocoa butter to absorb water can be improved by adding Tween-61, a non-ionic, waxy, solid, tan surfactant.

However, cocoa butter has a lot of useful advantages, including having a soft base that doesn't irritate sensitive membrane tissues, being widely accessible, being easy to use when making suppositories without the necessary tools, and being reasonably priced [7].

B. Cocoa Butter Substitutes

These are the starting materials created from various vegetable oils, including coconut or palm kernel oil, which are changed through the processes of etherification, hydrogenation, and fractionation to create products with various compositions and melting points. They can be created to decrease rancidity during long-term storage. This kind of suppository base mostly consists of combinations of saturated fatty acid triglyceride esters [8].

C. Witepsol

A white, waxy, brittle substance called “Witepsol”, melts into a transparent or yellowish liquid with almost any odour. Emulsifiers are included in it, allowing it to absorb a little amount of water. Witepsol comes in roughly 20 distinct variants, which are categorised into the H, W, S, and E series. Class H15 is the kind most frequently used in pharmaceutical practise. Its melting point ranges from 33.5 °C to 35.5 °C, which is rather near to its pour point range of 32 °C to 34 °C [8], [9].

D. Fatty Base

It is a solid that is opaque, white, waxy, and flavourless. Triglycerides from coconut oil and palm kernel oil are combined in this. They function as suspending and emulsifying agents. Melting temperatures for this base range from 32 °C to 36.5 °C. The base should be gently and consistently heated to 49–54 °C, not exceeding the required temperature, before adding the active medicinal components. When the liquid reaches a temperature of 43 to 49 °C, suppositories should be poured [8], [10].

E. Supposiblend

It is a granular version of the triglyceride basis for suppository, which is a combination of fatty acids derived from vegetable oils like palm kernel oil. These don't have a cocoa butter polymorphism and are oxidation resistant. It melts at temperatures between 34 and 37 °C [8], [10].

F. Polyethylene Glycol (PEG)

These are blends of polymers made of polyethylene glycol with various molecular weights. Surfactants and other additives, such as polyethylene glycol bases, are sometimes used in commercial suppositories. One of the most popular bases is Polybase, made by Paddock Labs in the US, and PEG blend, made by Gallipot Inc. in the US. Both comprise a combination of polyethylene glycols together with the emulsifier polysorbate-80. Polyethylene glycol bases must be moistened with water prior to use since they are often produced in a way that prevents them from melting at body temperature and instead dissolving in bodily fluids [11].

V. Improvement in Medication

Suppository leakage from the vagina or rectum while having a solid dosage form is a serious issue in terms of user acceptability. The process of administering medication from a suppository entails first transforming the solid into a semisolid state, and then, when the suppository dissolves or melts, into a liquid condition. Most women have cited leakage as a key worry with acceptability [12]. Therefore, the melting/dissolving suppository is given additional yield-stress qualities during suppository production by the introduction of mucoadhesive excipients like Carbopol (lubrizol), and the suppository's components will only spread and flow under strains. This would stop vaginal leaking brought on by gravity and stop retrograde flow that causes first pass metabolism [13]. And from here onwards the improvement in suppositories started.

VI. Modern Concept of Medication

A. Bi-layered Suppositories

A revolutionary method called a "bi-layered suppository" was created to combine two or more active components in a single dosage form for sequential drug release and to prevent incompatibility. By localizing the medicine to the site of action, lowering the dosage needed, or ensuring uniform drug distribution, controlled delivery systems aim to minimize the frequency of dosing or enhance the efficacy of the treatment while simultaneously enhancing patient compliance and convenience. Controlled release medication delivery's main goals are to increase patient compliance, assure patient safety, and enhance treatment efficacy. Bi-layered suppositories were created with the primary goals of administering fixed dosage combinations of several medications, separating incompatible medications from one another, and managing the pace at which one or more medications are delivered. Comparing bi-layered suppositories to traditional mono-layer suppositories reveals some significant benefits. For instance, bi-layered suppositories' sequential release of two medications can save the repeated dosing necessary by conventional dosage forms, and physical separation can avoid the incompatibility of two or more pharmaceuticals. Additionally, bi-layered suppositories have made it possible to create dosage forms with controlled distribution of active medicinal components by combining layers with different release patterns or layers with gradual release and layers with fast release [14]–[17].

B. Ideal Characteristics of Bi-layered Suppositories

Bi-layered suppositories have to be classy and devoid of flaws like chips, fractures, discoloration, and contamination. It must be able to release the therapeutic compounds in a desirable, predictable, and repeatable manner and possess the necessary chemical and physical stability to preserve its physical properties over time. Additionally, bi-layered suppositories need to be strong enough mechanically to

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endure shock during manufacture, packaging, shipping, and administration [18], [19].

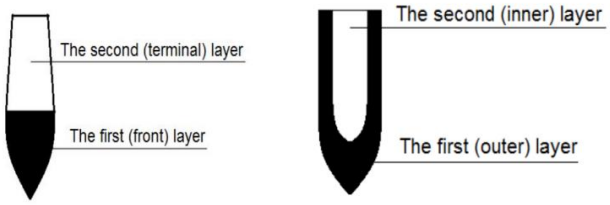

Fig. 3. Showing First and Second Layer of Suppository.

TABLE I: SHOWING LIST OF VARIOUS ADVANCES MADE IN BI-LAYERED SUPPOSITORIES

Author(s)	Active ingredient(s)	Rational	Year	Ref. no.
Mohamed ali *et al.*	Paracetamol and metoclopramide HCL	Combination therapy	2017	[14]
Marsovna *et al.*	Paracetamol and licorice extract	Combination therapy	2015	[15]
Phaechamud *et al.*	Propranolol HCL Probiotic (lactobacillus sp.)	Sustained release Combination therapy (vaginal route)	2013 2012	[19]
Kale *et al.*	Probiotic (lactobacillus sp.) and Prebiotic (organic acid)	Combination therapy (vaginal route)	2012	[20]
Ramadan Patayan Soliman *et al.*	Diclofenac Sodium Lactobacilli and antibacterial herbal extract	Bioavailability improvement and combination therapy (vaginal route)	2012 2011	[21] [22]
Chicco *et al.*	Paracetamol	Bioavailability improvement	1999	[16]
Yahagi *et al.*	Lidocaine	Bioavailability improvement	1999	[18]
Iwata *et al.*	Progesterone Paracetamol, aminophenazone	Sustained release	1997	[23]
Realdon *et al.*	Aminophylline	Modulating drug release	1997	[24]
Deshmukh and Thwaites	Diazepam	Fast release	1989	[25]

C. Homogeneous Plain Suppositories

The anal and vaginal suppositories are homogeneous common suppositories based on how they are administered. Torpedo-shaped ones are the easiest to insert to the rectum and are more able to adjust to the anal sphincter's contraction. Suppositories are often used in adults at a weight of 2 g and a length of 3 to 4 cm, and in children at a weight of 1 g, reduced as necessary for age. Vaginal plugs were typically spherical, ovoid, duckbill, or fusiform in shape, weighing 2 to 5 g and having a diameter of 1.5 to 2.5 cm. Urethral plugs, nose plugs, ear plugs, and other varieties of suppository exist as well.

D. Double Layered Suppositories

A double-layered suppository consisting of a water-soluble matrix plug and a drug-containing plug was developed to enable the efficient absorption of suppository medications in the lower rectal vein. The characteristics can be classified as follows creating suppositories with upper and bottom two layers by distributing two or more medications with distinct physicochemical qualities into a lipid soluble mechanism or a water-soluble mechanism, respectively, to facilitate drug absorption or prevent potential drug compatibility contraindications. The upper layer of blank matrix was used to block the upward diffusion of drugs, thereby reducing drug absorption from the superior rectal vena cava, improving drug availability and minimizing drug side effects. The upper and lower layers were made with blank matrix and drug-containing matrix, respectively. In order for suppositories to have both immediate and sustained release effects when used, a drug is prepared as upper and lower two layers by dispersing in a lipid soluble matrix and a water-soluble matrix, respectively. Suppositories from the inner and outer bilayers can exert the effects of both drugs because the outer layer dissolves first, followed by the inner layer, which dissolves and fuses. Aspirin bilayer suppositories were made with a water-soluble matrix for the top blank layer and a lipid-soluble matrix and fatty acid glycolipids for the bottom therapeutic layer. Improve aspirin's bioavailability and effectively stop the upward diffusion of pharmaceuticals released by conventional aspirin anal suppositories. Also, block certain medications from entering the body through the portal hepatic system. In order to create a new double layered suppository that is both safe and long acting for the treatment of gynecological inflammation, [26] prepared double layered suppositories using bitter bean extracts for local vaginal delivery. He then used the slow-release characteristics of double layered suppositories to prolong the retention time of drugs and exert long-lasting and stable drug effects [27].

E. Hollow Suppositories

In 1984, Tandou Shanfeng created hollow suppositories (HTS), which include an exterior layer composed of matrix and a hollow centre that may be filled with medications in a variety of forms, including solid, liquid, and suspended. Given its quick drug release, excellent bioavailability, and broad applicability range compared to conventional suppositories, states, HTS presents the option of rectal drug administration for numerous medications. Hollow rectal plugs increase systemic efficacy of medicine administration. To fast attain the effective blood drug concentration and maintain the concentration for a long period, nemesulide is made into a hollow suppository. This indicates that this hollow suppository not only allows for the rapid onset of drugs and the maintenance of treatment for a longer period of time, but also has a slower peak blood concentration and reduces drug toxic side effects. [28] investigated the in vitro dissolution of the home made hollow plugs using pediatric ibuprofen plugs that were supplied commercially as a control. The findings demonstrated that both hollow plugs reached dissolving equilibrium with dissolution rates above 90% in less than 20 minutes. However, the dissolution rate was only 79% by 70 minutes, suggesting that the hollow plug could be able to release drugs quickly [29].

F. Microcystic Suppositories

Microcapsule plugs offer prolonged release, minimal toxicity, constant blood concentration, and lengthy maintenance times over conventional plugs. In vitro cumulative drug release rates of naproxen microcapsule plugs, and ordinary naproxen plugs were evaluated by [30] It shown that making naproxen microcapsules was an easy, quality-controlled procedure with a longer lasting impact. Acetaminophen (AAP) microcapsules were created by [31] using aggregation technique, and there in vitro drug release

behavior was examined. In comparison to conventional suppositories, the produced composite microcapsule plugs exhibit improved drug release properties.

G. Effervescent Suppositories

Effervescent Suppositories, as opposed to regular suppositories, are more suited for treating gynecological conditions since they may generate huge amounts of foam after disintegrating, increasing the drug's surface area in contact with the lesion and improving its efficacy. Semi-synthetic fatty acid glycerides were employed as the suppository matrix, sodium bicarbonate, citric acid as the foaming agent, and danazol as the primary medication to make effervescent plugs. The produced foam increased the drug concentration in local tissue, which in turn improved the therapeutic effect of the drug. Povidone iodine, sodium bicarbonate, citrate, and duckbill-shaped suppository moulding were used to prepare povidone iodophore plugs, and it was discovered that this method was straightforward, stable, and convenient for quality control. It also had a long validity period of 432d and did not affect the iodine content when stored at low temperature [32].

H. Sponge Suppositories

Sponge suppositories, which are often vaginal, have a longer shelf life than conventional suppositories because they may be spread over the mucosal surface of the luminal tract repeatedly without melting the matrix. The typical matrix is gelatine, and the generated suppositories can be easily used by being enzymatically absorbed in the body. Reference [33] created a sponge-shaped vaginal plug containing tinidazole, and in vitro testing showed that it had a slow-release action. Clinical observations have indicated that this formulation has good effectiveness, a short treatment time, and few adverse effects, making it useful for broad usage. Reference [34] showed that metronidazole vaginal sponge suppositories based on polyether type polyurethane foam were more durable, secure, and practical to use than metronidazole suppositories based on polyethylene glycol.

I. Gel Suppository

Due to the gels' unique adhesive force to the biological mucosa, which can extend the retention and release time of drugs to promote drug absorption and enhance bioavailability, compared to conventional suppositories, the foreign body sensation that results from the incorporation of suppositories into the body cavity can be avoided. Reference [35] used white clear gelatinous semi-solid water-soluble gel composite tinidazole hydrogel plugs fabricated from tinidazole, chlorhexidine acetate, clotrimazole with matrix poloxamer P407, Carbomer and other excipients processed by advanced processes to improve the traditional suppositories' inability of sustained and constant drug release and susceptibility to body temperature, which resulted in liquid like efflux of matrix after thawing and contaminated clothing. The Compound Tinidazole hydrogel plug has a high local concentration in the vagina after use, no adverse effects have been reported at this time, and it can be released continuously in a stable manner to achieve sustained release.

J. Sustained Release

Suppositories The medication must first diffuse out of the insoluble matrix and release gradually through the dissolving influence of mucosal fluid in suppositories created by encapsulating medicines in a plastic-based, non-soluble polymeric substance. This delays the dissolution and release of the drug. It was discovered that the formulation of the indomethacin sustained release suppository had a distinct sustained release profile, a delayed time to peak, and a lower peak concentration when compared to conventional suppositories, Reference [36] prepared sustained-release suppositories using metronidazole and miconazole nitrate as the main drugs, hydroxypropyl methylcellulose as the backbone material, and a hot-melt method, which can not only prolong drug efficacy and reduce administration frequency, but also flatten drug release and maintain effective drug concentrations to maintain treatment [37].

VII. Conclusion and Outcomes

After gone through literature of lots of review and research paper, which has been taken from different search engines like Google Scholar, PubMed, Scopus, Science Direct etc., a review paper is being prepared based upon the evidence that has been provided by the different authors in the different journals. This article is provided with the description of suppositories, their shapes and sizes which are available in the market or till the date it has been formulated. This article also contains descriptions of the different types of suppositories or different dosages form of suppositories which have already been discovered and have shown successful treatment against particular type of disease. In this article, an analytical review of the assortment of modern suppository bases with a description of their physical and chemical properties, advantages and disadvantages was carried out. Not only these, but in addition, it is provided with the ideal property of bases, advantages of suppositories along with their applications and methods of preparation of suppositories. Moreover, it gives us descriptive information on the newer concept and advancement on various kinds of suppositories formulations which has shown significant achievements in treating various diseases or disorders. The current work signifies the importance of suppositories over the other dosage forms and has been concluded that it avoids first pass metabolism, shows local and systemic effect, accommodates the patient who possess difficulty in oral administration and increased bioavailability. Its structure does not cause discomfort because it melts as soon as it comes in body cavity due our body temperature. It also has one of the great advantages in administrating the medication to the unconscious patient, easy to use for pediatrics and geriatric patients. And can also be administrated to the old or the mentally disturbed patient via rectal route.

Summarizing the overview on suppository, composition, shapes and sizes, methods of preparation, mechanism of action, types of bases of suppositories, newer concept, and advancement in the formulation of suppositories might help the researchers. In the future it will make it possible to choose a suitable excipient in order to create new medicines in the form of suppositories. The suppository may be useful as a

Sustained-release, Bi-layered, muco-adhesive and many more formulation for the long-term treatment of chronic disease like essential hypertension, asthma, diabetes, AIDS, anemia, etc., as well as for the treatment of pregnancy, chemotherapy and allergy included emesis. Now days, it has its application as local and aesthetics, laxatives, local antibiotic treatment. Form the future point of view, there are many on-going work or research are already being directed on various authorized labs or at research centre in all over the world. Recently they have been working on INSULINE THERAPY in suppository form and also for ANTI-HIV and the result is coming out to be promising. Hope for better outcomes in the coming years.

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CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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