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Original Article

INVESTIGATING THE ROLE OF NANOPARTICLE-BASED CURCUMIN IMPLANTS IN PREVENTION OF POST-LAPAROTOMY PERITONEAL ADHESION: AN *IN VIVO* STUDY

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ABSTRACT

Objective: The objective of this research is to develop a controlled-release drug delivery system for relieving peritoneal adhesion. The system is designed to utilize a polymer hydrogel incorporating Curcumin (cur) loaded Mesoporous Silica Nanoparticles (Msn). Its objective is to improve the properties of curcumin and reduce peritoneal adhesion after laparoscopic surgery.

Methods: The rats in each group underwent intra-abdominal adhesion modeling surgery and received the following implants: implants containing Msn loaded with cur (imp/Msn@cur), Implants Containing Cur (imp/cur), implants containing Msn without cur (imp/Msn), Implants without Msn and cur (imp) and group only modeled (contrl). After 14 d, the surgical site was reopened and the specimens were evaluated by gross processing and histology staining for adhesion band formation, fibrosis, and inflammation. Data were analyzed by SPSS v.22 using Fisher's exact test, one-way ANOVA, and Tukey's test and $P<0.05$ was considered statistically significant.

Results: The number of vascularized or non-vascularized adhesion bands was evaluated According to the results, the number of vascular bands in the control group was only significantly higher than the other groups ($P<0.001$). Also, the mean number of vascular adhesion bands in the imp group was significantly higher than the other intervention groups ($P<0.001$). All studied rats in the contrl group had adhesions and the severity of adhesions in this group was higher than the others. Also, in the imp/Msn@cur group, the severity of adhesion was the lowest than the other groups.

Conclusion: The research findings indicated that utilizing implants with cur-loaded Msn resulted in improved peritoneal adhesion and reduced collagen bandages following laparotomy.

Keywords: Curcumin, Peritoneal implant, Mesoporous silica nanoparticles, Controlled release

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INTRODUCTION

The formation of peritoneal adhesions is the most common complication following abdominal and pelvic surgeries, affecting a significant number of patients. Small bowel obstruction, infertility, chronic abdominal pain, and prolonged surgical time, as well as an elevated risk of bowel perforation during preoperative surgery, are some of the potential consequences that can arise from peritoneal adhesions [1–4]. It is crucial to address and manage peritoneal adhesions effectively to minimize their detrimental effects on patients' health and well-being. While the utilization of laparoscopic surgery and other surgical advancements can indeed reduce the likelihood of adhesion formation, it is important to acknowledge that minimally invasive procedures may not always be suitable or feasible. As a result, intraabdominal adhesions continue to pose a considerable challenge, leading to significant morbidity and placing a substantial strain on healthcare resources [5]. Curcumin (cur) is a naturally occurring polyphenol extracted from the rhizome of the Curcuma longa plant. In recent years, extensive research conducted in both laboratory settings and living organisms has consistently demonstrated the exceptional properties of cur, including its ability to combat cancer, viruses, arthritis, oxidative stress, inflammation, etc [6–10]. The anti-inflammatory properties of cur are attributed to its ability to regulate the signaling pathways implicated in inflammation and hinder the synthesis of inflammatory mediators [11]. Multiple recent studies have indicated that cur could potentially serve as a viable treatment option for peritoneal adhesion [5, 12, 13]. Cur has a remarkably low solubility in water, measuring only 11 ng/ml, which stands as a significant hindrance to its pharmaceutical function [14, 15]; hence, nanoparticle-based drug delivery systems could be utilized as a potential solution for this complexity. Mesoporous Silica Nanoparticles (Msn) represent a highly promising category of porous materials that exhibit remarkable surface properties, such as a high specific surface area and well-defined pore size. Apart from their favorable surface characteristics, Msn also demonstrates excellent biocompatibility, controllable size, and facile surface modification, among other attributes. Consequently, they emerge as highly suitable contenders for a wide range of biomedical applications [16-18]. Biodegradable polymers have revolutionized the medical field for over 50 years, leading to significant advancements in drug delivery, biomaterials, tissue engineering, and medical device development. The progress made in macro-and micro-drug-delivery systems has opened doors for the creation of controlled-release nano-drug delivery platforms, which have the potential to overcome pharmacological limitations and provide substantial advantages over conventional dosage forms [19]. In recent years, the main emphasis of research in treating peritoneal adhesion has focused on using anti-peritoneal adhesion biomaterials in different physical forms. Natural and synthetic biocompatible polymers have shown promise in fighting against peritoneal adhesion in animal trials. Some biomaterials, such as Seprafilm and Adept, have been authorized for clinical application. Nevertheless, it is crucial to recognize that these materials have not shown complete efficacy in preventing peritoneal adhesion development [20]. In this investigation, our objective is to develop a controlled-release drug delivery system utilizing a Hydroxypropyl Methylcellulose (HPMC) polymer hydrogel that incorporates cur-loaded Msn. The purpose of this platform is to enhance the pharmaceutical characteristics of cur and alleviate peritoneal adhesion after laparoscopic surgery.

MATERIALS AND METHODS

Chemicals and reagents

hematoxylin, eosin, and neutral buffered formalin 10% were purchased from Sigma Aldrich. Additional reagents and solvents were acquired from Merck (Darmstadt, Hesse, Germany).

Implant characteristics

In this research, we utilized the intraperitoneal implant that was synthesized and characterized in a recent study conducted by Dhiya Altememy *et al.* [21]. The implant was fabricated using the molding technique and composed of HPMC polymer infused with cur-loaded Msn. According to the results of this research, MSN was synthesized using the sol-gel method, and they have a diameter ranging from 50 to 100 nm and a polydispersity index of 0.285. The x-ray diffraction results revealed MSN index peaks at 2.25, 4.1, and 5.1, indicating that the nanoparticles have crystalline structure and are hexagonal in nature. The surface area is 778.73 m2/g according to the BET analysis results, and the presence of mesoporous particles with a pore radius of 1.64 nm was confirmed by the BJH analysis results, which is consistent with MCM-41 nanoparticles. The prepared different formulation implants had a uniform, smooth, and bubble-free surface, opaque and yellow color. Additionally, the fabricated implants exhibited a 6-hour surface pH range of 7.05-7.27, a disintegration time range of 56.66±1.52 to 60.66±4.04 min, and also bioadhesive strength range of 162.66±10.40 to 185.66±46.33 N.

Animal experiment

In this study, a total of 40 male Wistar rats weighing between 200 and 250 gs were utilized for the experiment. Experimental animals were obtained from the Pasteur Institute of Iran and were adapted for 1 w before surgery. Standard lab procedures were followed when caring for the animals. The National Institutes of Health's (NIH) Guidelines for the Care and Use of Laboratory Animals (NIH publication #80-23) and the institutional guidelines for animal care and use (Shahrekord University of Medical Sciences, SKUMS) with ethical code: IR. SKUMS. REC.1398.140 was followed throughout all procedures.

Study groups

The rats in each group underwent intra-abdominal adhesion modeling surgery and were subsequently administered various implants as outlined below:

1. Implants containing Msn Loaded with Cur (imp/Msn@cur)

2. Implants Containing Cur (imp/cur)

3. implants containing Msn without Cur (imp/Msn)

4 Implants without Msn and Cur (imp)

5. group only modeled without treatment (contrl)

Induction of experimental intra-abdominal adhesion

Adhesion lesions were created under general anesthesia. All surgeries were performed uniformly and standardly on all rats and by one person. For rat anesthesia, intraperitoneal injections of 80 mg/kg ketamine and 10 mg/kg xylazine were done. After clipping the abdominal hair of the rats, the skin of the surgical site was prepared aseptically. An incision of 2 cm was made in the midline of the abdomen. After accessing the abdominal area, the end of the ileum and cecum were separated from the surrounding abdominal tissues and placed on a sterile wet sponge [22]. The cecum scratch model will be used to create adhesion; In this way, the cecum serosa will be scratched by a sterile sponge on the antimesenteric surface until small petechiae bleeding appears. In this stage, after returning the organs inside the body, either the mentioned implant was put inside the body cavity. Subsequently, the standard closure of the cutting site was done using a simple all-round pattern and 4/0 absorbable threads for the abdominal muscles area, but the muscles, fascia, and the animal's skin, which are not related to the inside, were placed with 2/0 non-absorbable silk thread. Once again, the skin was disinfected and the rats were placed at room temperature to recover. External sutures were removed on the seventh day of treatment.

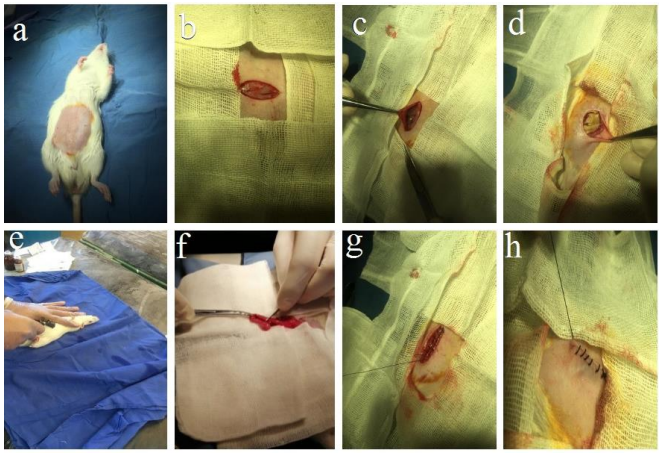

Fig. 1: Different phases of intra-abdominal adhesion modeling surgery

Treatment evaluation

After 14 d from the day of the lesions, laparotomy was performed again. For this purpose, after anesthesia, the abdomen of each rat was opened and the adhesions were graded by a person who was unaware of the grouping of the samples.

The scale provided below was utilized to compare the adhesions [23]. according to this scale, the degree of adhesion in the macroscopic examination was calculated as follows:

0 Without any adhesion bands

1 Single adhesion band between organs or between organs and the abdominal wall

2 Two adhesion bands, between organs or between organs and the abdominal wall

3 More than two adhesion bands between organs or between organs and the abdominal wall

4 organs directly adherent to the abdominal wall, regardless of the quantity and size of adhesive bands

Furthermore, for pathology (microscopic) examinations, a sample was separated from the existing adhesive tissue and placed in a 10% neutral buffered formalin fixative for 2 d. Tissue processing and molding were done with paraffin and wax, and cross-sections 5 µm thick were prepared by microtome with a fixed blade. The incisions

were stained with hematoxylin and eosin. Histopathological examinations were performed by a pathologist who was unaware of the grouping of the specimens using the Olympus-style microscope.

Statistical analysis

The obtained data were analyzed by SPSS v.22 software using Kruskal-Wallis and Mann-Whitney tests and P<0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The effect of implant preparation on intraperitoneal adhesion after laparotomy in rats

After 14 d of abdominal adhesion surgery modeling and placing the desired implants in the abdominal cavity of the studied groups, laparotomy surgery was performed again to evaluate the amount of abdominal adhesion. First, the number of vascularized or non-vascularized adhesion bands was evaluated as demonstrated in table 1. According to the results of table 1, the majority in all studied groups had no non-vascular band. According to Fisher's exact test, no significant relationship was observed between the number of non-vascular adhesion bands and the studied groups (P>0.05) (fig. 2B). The relationship between the number of vascular adhesion bands and the total number of bands within the studied groups is shown in table 1. According to the results of table 1, the number of vascular bands in the control group was only significantly higher than the other groups (P<0.001). Also, the mean number of vascular adhesion bands in the imp group was significantly higher than the other intervention groups (P<0.001). The mean number of vascular adhesion bands in imp/cur, imp/Msn@cur, and imp/Msn groups were not significantly different (P>0.05) (fig. 2A). Also, the total number of bands in the contrl group was significantly higher than the other groups (P<0.001). Also, the mean number of total bands in the imp group was significantly higher than other intervention groups (P<0.001). The mean number of bands in the remaining groups was not statistically significant (P>0.05) (fig. 2C).

Table 1: The relationship between the number of non-vascular adhesion bands in the studied groups and the comparison of the average number of adhesive bands with vessels and the total number of bands in the studied groups

Study group	Control	Imp	Imp/Msn	Imp/cur	Imp/Msn@cur	P value
Without any non-vascular adhesive bands	8(100%)	6 (75%)	8 (100%)	6 (75%)	5(62.5%)	0.212
Only one non-vascular adhesive bands	0 (0 %)	2 (25%)	0 (0%)	2 (25%)	3c(37.5%)	0.212
The mean number of vascular adhesions	7.38±1.3	5.00±1.2	1.63±1.19	1.13±0.84	0.75±1.04	0.000
mean total number of bands	7.38±1.3	5.25±1.4	1.63±1.19	1.13±0.52	1.13±0.99	0.000

Frequency percentage, Fisher's exact test One-way analysis of variance with Tukey's post hoc test Data are expressed as mean±SD, n=8

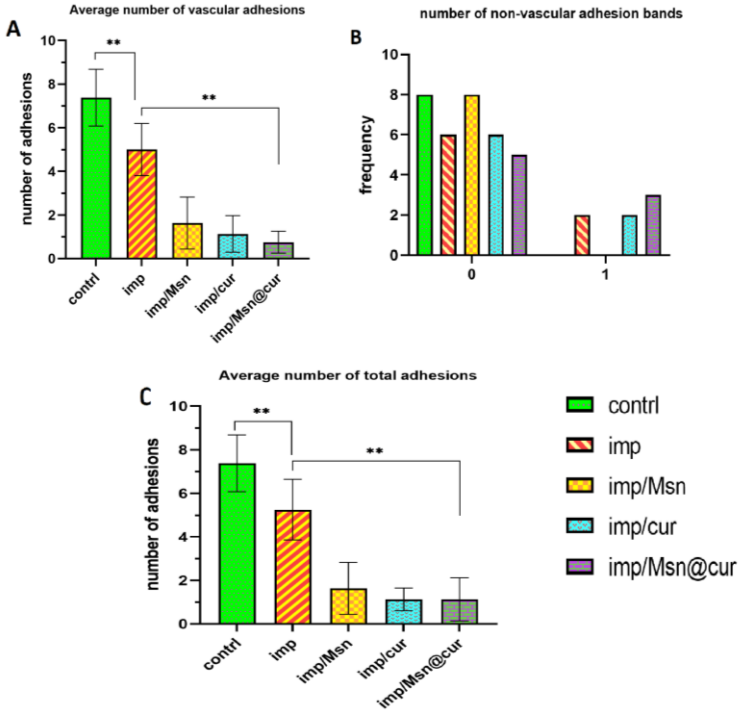

Fig. 2: (A) Average number of vascular adhesion bands, (B) Number of non-vascular adhesion bands, and (C) Average number of total bands in different study groups. Error bars indicate the standard deviation of replicates, n=8, and P<0.01**

The relationship between adhesion intensity and studied groups is shown in table 2. According to the results, all studied rats in the control group had adhesions and the severity of adhesions in this group was higher than the others. Also, in the imp/Msn@cur group, the severity of adhesion was the lowest than the other groups. Based on Fisher's exact test, a significant relationship was observed between the severity of adhesion with the studied groups (P<0.001) (table 2) (fig. 3A). The relationship between fibrosis severity and studied groups is shown in table 2. According to the results, the control group was the only group with the majority of fibrosis severity. As the imp/Msn@cur group, the severity of fibrosis in most rats was as low. In the imp/Msn group, the majority of fibrosis severity was moderate. Based on Fisher's exact test, no significant relationship was observed between fibrosis severity and studied groups (P>0.05) (table 2) (fig. 3B). The relationship between the severity of inflammation and the study groups is shown in table 2. According to the results, the severity of inflammation in the control group was low. In the imp/Msn@cur and imp/cur groups, the

severity of inflammation was moderate and in the imp/Msn group, the rate of inflammation was low. Based on Fisher's exact test, a significant relationship was observed between the severity of inflammation in studied groups (P<0.05) (table 2) (fig. 3C).

Table 2: Intensity of adhesion, severity of fibrosis, and severity of inflammation in different study groups

Intensity of adhesion	Control	Imp	Imp/Msn	Imp/cur	Imp/Msn@cur	P value
1	0(0.0%)	0(0.0%)	2(25%)	1(12.5%)	6(75%)	0.000
2	0(0.0%)	0(0.0%)	4(50%)	6(75%)	1(12.5%)	
3	0(0%)	6(75%)	2(25%)	1(12.5%)	1(12.5%)	
4	8(100%)	2(25%)	0(0%)	0 (0%)	0(0%)	
Severity of fibrosis	control	imp	imp/Msn	imp/cur	imp/Msn@cur	P value
0	3(37.5%)	2(25%)	2(25%)	1(12.5%)	3(37.5%)	0.601
1	4(50%)	2(25%)	1(12.5%)	3(37.5%)	2(25%)	
2	1(12.5%)	3(37.5%)	5(62.5%)	2(25%)	3(37.5%)	
3	0(0.0%)	1(12.5%)	0(0.0%)	2(25%)	0(0.0%)	
Severity of inflammation	control	imp	imp/Msn	imp/cur	imp/Msn@cur	P value
0	3(37.5%)	3(37.5%)	4(50%)	3(25%)	4(50%)	0.002
1	5(62.5%)	1(12.5%)	4(50%)	0(0.0%)	0(0.0%)	
2	0(0.0%)	6(75%)	0(0.0%)	4(50%)	4(50%)	

Frequency percentage is calculated. Fisher's exact test

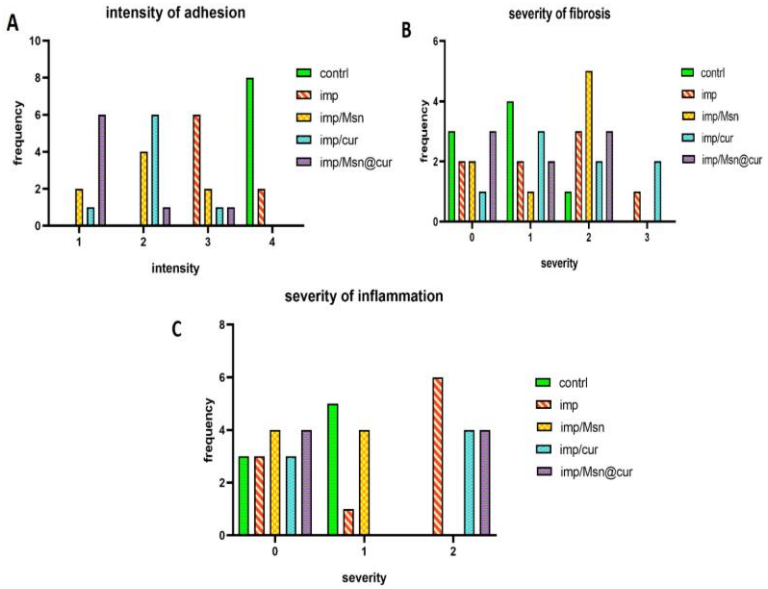

Fig. 3: (A) Number of Adhesion intensity frequency, (B) Number of fibrosis severity frequency, and (C) Number of inflammation severity frequency in the study groups

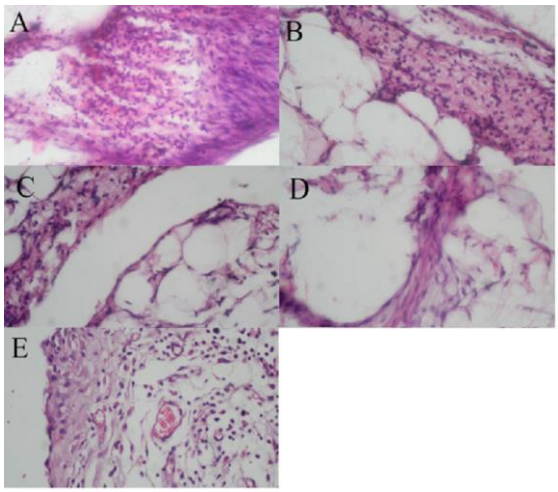

Fig. 4: Microscopic section image of adhesion bands in the studied groups (A) control, (B) imp, (C) imp/Msn, (D) imp/cur, and (E)imp/Msn@cur

Histopathological examination

Fig. 4 exhibits microscopic sections (100X magnification) of adhesion bands, which have undergone staining with Hematoxylin and Eosin. Fig. 4A displayed a moderate to severe infiltration of inflammatory cells with significant fibrosis and the formation of collagen bundles in the control group. On the other hand, fig. 4B exhibited fatty tissue with moderate inflammatory infiltration and focal fibrosis in the imp group. In contrast, the imp/Msn group showed fatty tissue with mild inflammatory infiltrate and focal fibrosis as shown in fig. 4C. Additionally, fig. 4D illustrated fatty tissue in the imp/cur group without significant inflammatory infiltration but with fibrotic bundles in the center of the image. Lastly, fig. 4E depicted the imp/Msn@cur group with connective and fat tissue containing mild to moderate inflammatory infiltration, edema, and slight fibrosis.

DISCUSSION

Millions of individuals worldwide experience a significant decline in their quality of life due to the presence of intraperitoneal adhesions following surgery. These adhesions can lead to various complications, such as small bowel obstruction, unintended enterotomy during adhesiolysis, pelvic pain, and even secondary female infertility. It is crucial to recognize that these complications not only result in morbidity but can also lead to mortality, highlighting the urgent need for effective management and prevention strategies [24]. The optimal approach to prevent postoperative adhesions involves minimizing or eradicating adhesions while preserving the natural process of wound healing [25]. Adhesion formation has been prevented through the utilization of barrier devices and pharmacological agents. Hydrogel implants have been recently employed for the administration of anti-inflammatory medication to prevent peritoneal adhesion [12, 26, 27]. In this research, the focus was on ameliorating intra-abdominal adhesion by utilizing implants that consisted of cur-loaded mesoporous silica nanoparticles. Therefore it is hypothesized that Nanoparticles have the potential to enhance the stability and biocompatibility of cur, thereby prolonging its circulation time in both the bloodstream and wound site. Consequently, this amplifies the antioxidant properties of cur, allowing for more effective utilization. The results of studies on the use of cur-loaded nanodrugs in the treatment of diseases and tumor cells have shown that nanodrugs can act specifically on the target cell and, especially in the case of cancer cells, have a higher toxicity to cancer cells than healthy cells [28]. Studies have also shown that nanoparticles are non-toxic and fully biocompatible. according to the data presented in table 1, The research results indicate that the average number of vascular adhesions in the contrl and imp/Msn@cur groups following laparotomy surgery was 7.38±1.3 and 0.75±1.04, respectively. These results indicate a significant decrease in the number of vascular adhesions following treatment with imp/Msn@cur. Furthermore, in comparison to the control group, the mean total quantity of adhesion bands was notably reduced within this particular group. As shown in Fig.4 tissue histopathological examination results indicate that collagen density, fibrosis, and severe inflammation were observed in the contrl group, while a decrease in fibrosis, inflammation, and less collagen deposit was observed in the study group that were treated with different implant formulations. Our results were consistent with the findings of recent studies [5, 29]. Studies that were performed on animal models have indicated that several medications, such as fibrin lubricants, corticosteroids, nonsteroidal anti-inflammatory drugs, and antioxidants, may reduce postoperative adhesions [30–32]. As previously stated, cur possesses a range of biological functions, including immunomodulatory, anti-inflammatory, antioxidant, antiviral, and anti-cancer properties. Given that these effects are associated with its anti-adhesion mechanisms, there is potential for cur to be utilized in conjunction with its anti-adhesive properties. Some studies have shown that pretreatment with cur has anti-apoptotic and cell protective properties in various tissues, which is probably due to its antioxidant, anti-inflammatory, and immune-modulating properties [33].

CONCLUSION

The current research assessed the impact of prepared implants on intraperitoneal adhesion after laparotomy in rats. The research findings indicated that utilizing implants with cur-loaded Msn nanoparticles resulted in improved adhesion and reduced collagen bandages following laparotomy, as opposed to implants lacking nanoparticles. This highlights the enhanced efficacy of nanoparticles in reducing intra-abdominal adhesions.

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AUTHORS CONTRIBUTIONS

Pegah Khosravian, Moosa Javdani, Hossein Amini-Khoei, and Mehrdad Karimi designed the experiments and discussed the results and strategy; Parisa Mehreganzadeh performed experiments and collected data; Fatemeh Driss analyzed data; Pegah Khosravian Supervised, directed and managed the study and Mohammad Amin Kaboli, Dhiya Altememy and Pegah Khosravian final approved of the version to be published.

CONFLICTS OF INTERESTS

The authors confirm that they don't have conflicts of interest.

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