Synergic fabrication of titanium dioxide incorporation into heparin-polyvinyl alcohol nanocomposite: enhanced in vitro antibacterial activity and care of in vivo burn injury

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Abstract
In this study, a highly porous heparin-polyvinylalcohol@TiO₂ nanocomposite (H-PVA@TiO₂) bandage was fabricated by incorporating TiO₂ into H-PVA hydrogel for burn injury. The effects of the H-PVA hydrogel and TiO₂ nanoparticle composition on the functional group and surface properties of the as-prepared bandages were characterized by Fourier transform infrared spectroscopy (FT-IR) and x-ray diffractometry (XRD). The morphology of the H-PVA hydrogel and H-PVA@TiO₂ were evaluated using a scanning electron microscope (SEM) and transmission electron microscope (TEM). A study of the material properties of H-PVA hydrogel has shown that the presence of TiO₂ nanoparticles improves its toughness. Prepared H-PVA@TiO₂ nanoporous dressing has indicated good antimicrobial activity against types of bacteria (Staphylococcus aureus and Escherichia coli) and excellent biocompatibility with human dermal fibroblast cells (HFFF2) suitable for biological applications. Additionally, in vivo experiments using Kunming mice showed it as-prepared H-PVA@TiO₂ nanocomposite dressings improved wound healing and triggered skin cell development alongside collagen growth. Synergistic effects of the H-PVA@TiO₂ nanocomposite hydrogel dressing material through in vivo experiments, such as its excellent hydrophilic design, strong bactericidal activity, biocompatibility and wound healing ability, make it a promising candidate for the treatment of burn injuries.

1. Introduction
Microorganisms such as bacteria, fungi, viruses, etc. infect human beings in daily life. The use of antimicrobial agents is essential to promote sterility and prevent infection. Burn injury is one of the most common and debilitating global health threats requiring urgent specialized treatment to reduce morbidity and mortality. Infection (including nosocomial infections) is the leading cause of death in burn patients as the compromised skin becomes the preferred host of pathogenic organisms [1–3]. Micro-organisms are the true object of illness, and their growing popularity is relatively high in or around the human being. Immediately after a burn, Gram-positive bacteria such as S. aureus primarily colonize the burn and, during the initial days of the injury, Gram-negative bacteria, including E. coli, colonize the surface of the burn [4–6]. Once in the body, these fast-growing microorganisms appear to form colonies. Micro-organisms can easily enter the body through ulcers and penetrate deeper into the tissues, causing an internal infection. The main purpose of wound healing is rapid recovery with minimal scarring and maximum function. A solution to the above damage is the use of bandages with a bactericidal effect [7–10].

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Hydrogels may be developed based on organic polymers or an organic combination. The nanostructured hydrogel dressings that have all the essential properties (outer layer of the injuries, special core, airflow, blood circulation, low toxicity, and environmental) [11–13]. Different forms of commercially available dressings are either made from nanomaterials (polymeric, heparin, amino acids, chitosan, benzoyl peroxide, polyethylene, collagen, etc.) or polymeric materials (alginate, poly-3-hydroxybutryrate, poly-L-lactic acid, polyvinyl alcohol, collagen, poly-caprolactone, polyvinyl alcohol, etc.) [14–16]. Heparin (Hp) is a normal sulphate macromolecule, commonly used with human systems. Hydrogels based on heparin or altered heparin have long been developed and examined. The heparin-based hydrogel was an effective tissue culture system with biophysical and biochemical in for the production of epithelial cells and chondrogenic and for the reconstruction of diversity in vivo. Polyvinyl alcohol (PVA) is a well-known biocompatible polymer that is commonly used in medication due to its favorable properties, such as water solubility, acceptable surface stability, and high genotoxicity [17–19]. Main work has been carried in situations whereby Hp and PVA (H-PVA) hydrogels were used to treat patients with severe wounds, bone tissue injury, etc. The goals of H-PVA-based skin treatment were easy availability, blood safety, low toxicity, and degradability. Even so, mentioned previously H-PVA dressings do not demonstrate antimicrobial growth, have a minimal therapeutic effect for wounds, and have poor mechanical reliability [20–22].

In this examination, flexible and porous bio–composite dressings using H-PVA hydrogel and TiO2 and their impact on wound infection have still not been reported. The present study is thus intended to test the effects of H-PVA@TiO2 nanocomposite dressings on contaminated tissue regeneration by using rats as experimental animals. The nanocomposite of H-PVA@TiO2 has a strong antibacterial effect against the two common organisms, namely S. aureus and E. coli. The healing behavior of the synthetic composite wrapping was assessed for thin waste burning in treated mice. Histological examination demonstrated the ability of the H-PVA@TiO2 nanostructure to regenerate tissue. This innovative nature of the wound dressing has potential for future medical applications.

2. Experimental methods

2.1. Materials

Heparin sodium salt from porcine intestinal mucosa ≥150 IU/mg (dry basis) was obtained from Qingdao Honghai Co. Ltd., China. Polyvinylalcohol was purchased from Sigma Aldrich. Titanium (IV) chloride (about 19% in toluene, about 1.0 mol l⁻¹) was purchased from TCI Chemical Co. All reagents used were used in analytical grade.

2.2. Synthesis of TiO2 nanoparticles

The formulation of nanocomposites was performed using the methodology described previously [23–26]. TiCl4 was applied dropwise to 80 ml of benzyl alcohol in a before-dried two-neck flask to a nitrogen atmosphere, accompanied by a swirling of the solution for 30 min respectively. The solution was poured for 24 h at 80 °C. The subsequent instigated white TiO2 accumulation was extracted, washed repeatedly with methanol to eliminate by-products, and washed for 1 h at 100 °C. TEM was used to analyze the size and shape characteristics of the nanocomposites.

2.3. H-PVA hydrogel preparation

The composite hydrogel was prepared by a single pot method. Briefly, 240 mg of polyvinyl alcohol was stirred in 7.5 ml of acetic acid until a uniform solution was formed. A 1.6 ml heparin sodium salt solution containing 3.4 ml of polyvinyl alcohol solution at a 1:2 ratio was stirred with a homogenizer (ITK® Ultra Turrax T18 basic) at 10000 rpm for 2 min to form a suspension. Thus, the H-PVA hydrogel was successfully prepared by a simple and easy process. All gel samples were stored at 4 °C. Before performing mechanical tests, the gel samples could remain at room temperature for approximately 30 min [27–29].

2.4. Preparation of H-PVA@TiO2 nanocomposite

Synthesized TiO2 nanoparticles were dispersed in deionized water. A 1% aqueous suspension of TiO2 nanoparticle solution was transferred to the H-PVA hydrogel, and the mixture was stirred at 300 rpm in an incubator at −37 °C for 12 h. The homogenous H-PVA@TiO2 nanocomposite was moved to Petri dishes for overnight storage at −37 °C. The resulting H-PVA@TiO2 nanocomposite bandages were used to treat wet wounds while lyophilized for one day at −37 °C for physicochemical characterization [30–33].
2.5. In vitro biodegradation and swelling studies

To study the biodegradation of the H-PVA hydrogel and H-PVA@TiO₂ nanocomposite, 0.5 g (W₁) of H-PVA hydrogel dried powder and H-PVA@TiO₂ nanocomposite were immersed in 50 ml of phosphate-buffered saline (PBS) and incubated at 37 °C for 7 days. Concurrently, a blank determination was performed in PBS on the same sample without the nanocomposite. After a period of 1, 4, and 7 days, the samples were washed several times with deionized water and dried in the oven at 40 ± 1 °C for 24 h.

The swelling ratio of the H-PVA hydrogel and H-PVA@TiO₂ nanocomposite were measured according to the described methods [34–36]. To measure the water sorption potential of the H-PVA hydrogel and H-PVA@TiO₂ nanocomposite, 0.1 g of dried powder of H-PVA hydrogel and H-PVA@TiO₂ nanocomposite were immersed in 30 ml of PBS with the desired pH at room temperature for 16 h to achieve maximum swelling equilibrium, then removed and gently pressed between filter papers and weighed.

2.6. Antibacterial activity

The antibacterial activity of the control, H-PVA, and H-PVA@TiO₂ was assessed with both Gram-positive and negative bacteria (S. aureus and E. coli, respectively). All bacterial cultures were obtained from the American type culture collection (ATCC, Manassas, VA, USA). First, 5 ml of nutrient agar was divided into 50 × 15 mm Petri dishes and 100 µl of S. aureus and E. coli bacterial solution was distributed over the surface of the growth medium. The microorganism volume was 10⁴ colony units ml⁻¹. Agar plates with the lawn of selected pathogens and the discs were incubated at 37 °C for one day. The colony counts were calculated to verify the bactericidal activity. The antibacterial activities of each sample were repeated three times [37–39].

2.7. Human dermal fibroblast cells (HFFF2)

The viability of the H-PVA and H-PVA@TiO₂ samples was assessed on human dermal fibroblast cells (HFFF2) using the MTT test [3–4, 5-dimethyl-2-thiazolyl]–2, 5-diphenyltetrazolium]. The cell concentration of 1 × 10⁵ cells ml⁻¹ was transferred to 96-well tissue culture plates after 12 h. After the incubation period, 100 µl medium was mixed with MTT (1 mg ml⁻¹) for 4 h. The MTT solution was carefully replaced and 150 µl of DMSO was added to each well. The fibroblast cells with H-PVA and H-PVA@TiO₂ samples were then incubated for the period of 1, 4, and 7 days and the MTT (Invitrogen, USA) test was performed. The optical density was determined at 490 nm with a microplate spectrophotometer.

2.8. In vivo animal study

The in vivo animal research was supported by the Laboratory Animal Center at Cangzhou Central Hospital in China. Kunming mice (males), weighing approximately 100 g and six weeks old, were used in this study. On the day of injury, each mouse was anesthetized with an injection of ketamine hydrochloride and full-thickness round wounds with an area of 2.5 cm² were made. The top part of the mice’s hair was removed and the functional part of the skin was hygienic. In this study, a full-thickness excision wound model was generated to assess the healing performance of H-PVA and H-PVA@TiO₂. The arranged wounds were then covered with the nude wound (negative control) H-PVA and H-PVA@TiO₂. The animals were killed under anesthesia and the wounds were dissected for histological examination at the end of the 14th day after the injury. The whole wound tissue with adjacent normal skin was obtained on days 7 and 14, immersed in paraformaldehyde buffered at 4% to fix the tissue with adjacent normal skin was obtained on days 7 and 14, immersed in paraformaldehyde buffered at 4% and taken up with paraffin, sliced, and stained with hematoxylin and eosin. All mice were housed separately to avoid additional effects on the wound area.

3. Results and discussion

3.1. Optical and surface analysis

The prepared TiO₂ nanoparticles were characterized using various techniques. Figure 1(A) shows the UV-visible spectrum of TiO₂ nanoparticles with a broad peak at ~292 nm, indicating the polydispersed nature of TiO₂ nanoparticles. The H-PVA hydrogel characteristic peak, with a significant blue-shift at 323 nm and a new peak of H-PVA@TiO₂ nanocomposite bandage at 250 nm. The inset of figure 1(A) shows photographs of the H-PVA hydrogel and the H-PVA@TiO₂ hydrogel nanocomposite suspension, respectively.

FTIR spectroscopy was used to find the occurrence of certain chemical bonds or functional groups in the H-PVA hydrogel, TiO₂, and H-PVA@TiO₂. The FTIR spectrum in figure 1(B), shows that the characteristic peaks of the H-PVA hydrogel are mainly due to the pyranose ring, saccharin structure, amide, glycoside bond, –CH, and –OH stretching, and the sulfated group (SO₃⁻). The amide band I or C = O, and the bending amide band II or NH appear at 1658 cm⁻¹ and 1586 cm⁻¹, respectively. The peak at 2950–2800 cm⁻¹ corresponds to the typical –CH stretching vibrations. The wide peak at 3500–3200 cm⁻¹ corresponds to the inter- and intramolecular hydrogen bonds that extend over –OH and –NH. However, the intensity of the characteristic
peak of amide II decreased sharply and a new peak emerged at 1028 cm$^{-1}$ - the characteristic peak of the SO$_3^-$.

The results provided evidence for the complexity of H-PVA hydrogel compared to heparin and PVA. The FTIR spectrum of TiO$_2$ in figure 1(B) clearly showed the three bands at 3400 and 1630 cm$^{-1}$, which correspond to the O-H stretching and bending vibrations of TiO$_2$ on the surface and adsorbed water molecules (Ti–OH). A band between 800 and 414 cm$^{-1}$ corresponds to the stretch mode of the Ti–O bond of TiO$_2$. Figure 1(B) shows that the H-PVA@TiO$_2$ nanocomposite was assigned with bands similar to the H-PVA hydrogel, although new broadband was observed at 655 cm$^{-1}$, which was the characteristic of TiO$_2$ stretching frequency. Thus, the FTIR spectrum (figure 1(B)) of the H-PVA@TiO$_2$ nanocomposite demonstrated the successful incorporation of TiO$_2$ into the H-PVA hydrogel.

XRD spectra in figure 1(C) showed that the characteristic planes of TiO$_2$ nanoparticles and the H-PVA@TiO$_2$ nanocomposite hydrogel were present in the 2$\theta$ range of 10°–80°. The H-PVA hydrogel XRD pattern exhibited 2$\theta$-peaks at 25.43°, 30.59°, 31.97°, and 41.99° and the TiO$_2$ XRD pattern exhibited sharper and stronger corresponding 2$\theta$-peaks at 25.35°, 38.41°, 47.25°, 50.85°, 60.59°, 70.83° and 76.85° that were in good agreement with the lattice structure as presented in figure 1(C). The sharp diffraction peaks indicated a higher degree of crystallinity for TiO$_2$ (JCPDS Card No.21-1272). As the TiO$_2$ was mixed adequately with the H-PVA hydrogel solution while preparing the H-PVA@TiO$_2$, a reduced intensity was observed in the H-PVA@TiO$_2$ XRD pattern for the characteristic 2$\theta$-peaks of TiO$_2$ and H-PVA hydrogel at 25.97°, 31.27°, 34.44°, 36.25°, 47.54°, 54.58°, 62.84°, 72.60°, and 76.97° (figure 1(C)).

### 3.2. Morphological analysis

Transmission electron microscopy-selected area electron diffraction (TEM-SAED) measurements were used to confirm the presence of TiO$_2$ nanoparticles in the as-prepared solution and to study the particle geometry (figure 2(A)) to compile a histogram of the particle size distribution (inset figure 2(A)). The corresponding SAED pattern (figure 2(B)) revealed that the TiO$_2$ nanoparticles have a polycrystalline structure, which was in good agreement with the XRD results. The micrographs indicated the successful synthesis of TiO$_2$ nanoparticles of less than 100 nm size and spherical structure formed as non-agglomerated and well-dispersed vast nanoparticle aggregates in the H-PVA hydrogel (figures 2(A) and (B)).
Scanning electron microscopy was used for the investigation of the shape, size, and morphology of the hydrogel matrices. Figures 2(C) and (D) shows the SEM micrographs of the H-PVA and H-PVA@TiO2 bandage as-fabricated. H-PVA had an organized fibril network with an abundance of empty spaces, as shown in the cross-section morphology. The SEM image of the H-PVA hydrogel revealed a smooth and porous surface (figure 2(C)). Pore connectivity plays a critical role in the rapid swelling of hydrogels. Moreover, the TiO2 nanoparticles were uniformly dispersed in the H-PVA hydrogel bandage, demonstrating well-interconnected pores with a size ranging from 50 μm to 150 μm (figure 2(D)). The distribution of TiO2 nanoparticles was rather homogenous, which indicates the pronounced mechanical, thermal, and biological properties of H-PVA@TiO2 composites.

3.3. Mechanical properties
To confirm the integrity of the membranes, the mechanical properties of the hydrogel and nanocomposite are important for effective dressing applications [40]. The mechanical properties (tensile strength, maximum elongation, and tensile modulus) of the pure materials (heparin and PVA), the as-prepared H-PVA hydrogel, and H-PVA@TiO2 are illustrated in figure 3(A). It is noted that the addition of TiO2 to the H-PVA hydrogel had a variable effect on the tensile strength and total elongation. The H-PVA hydrogel and H-PVA@TiO2 exhibited a tensile strength of 2.2 ± 0.6 and 2.9 ± 0.4 MPa, respectively, which was sufficient for tissue covering the wound. (figure 3(B)). The improved tensile strength ensures greater fracture toughness of the samples. These results demonstrated that the H-PVA@TiO2 nanocomposite has good mechanical properties suitable for use in biomedical applications. The elongation at break values represents the flexibility of the H-PVA hydrogel and H-PVA@TiO2 bandage. Pure heparin, PVA, the as-prepared H-PVA hydrogel, and H-PVA@TiO2 exhibited an elongation in the range from 20% to 50% at the fracture points (figure 3(C)). Figure 3 shows that the tensile strength increased with an increase in TiO2 concentration. The result of the tensile modulus (figure 3(D)) was consistent with the stress test. Overall, H-PVA@TiO2 demonstrated higher tensile modulus and elongation than heparin, PVA, and H-PVA hydrogel, however, it exhibited lower maximum strength. Therefore, flexibility would be an important consideration for the application of H-PVA@TiO2 nanocomposites for various types of the wound surface.
3.4. Biodegradation and swelling studies

Hydrogels have become the subject of improvement for use in many applications. The percentage weight loss (figure 4(A)) revealed limited degradation of the H-PVA@TiO2 bandages. All the as-fabricated bandages showed degradation of 24 to 27% (1 day), 39 to 48% (4 days), and 75 to 84% (7 days) after immersion in PBS medium, respectively. The presence of TiO2 reduced the degradation rate in the composite bands. This can be attributed to the interaction between the TiO2 and H-PVA hydrogel bandages. However, the as-fabricated bandage was degraded in vitro, while retaining its characteristics and form even after the 7th day in a situation without agitation of degradation behavior. The swelling of the H-PVA hydrogel and the H-PVA@TiO2 dressings were examined after 1, 4, and 7 days of incubation in PBS medium (figure 4(B)). Figure 4(B) suggested that H-PVA@TiO2 exhibited higher swelling capacity compared to pure H-PVA hydrogel bandages. Furthermore, the H-PVA hydrogel and H-PVA@TiO2 bandages showed similar swelling activity even after the addition of TiO2. An improvement in the swelling ability of H-PVA@TiO2 can be attributed to the presence of TiO2 nanoparticles of different sizes, morphology, and surface charges. Additionally, the formation of TiO2

Figure 3. Mechanical properties comparison of (A) Stress-strain curve (B) Tensile strength (C) Elongation (D) Tensile modulus of H-PVA and H-PVA@TiO2 hydrogel nanocomposite.

Figure 4. (A) Biodegradation and (B) Swelling ratio as-fabricated bandages of H-PVA and H-PVA@TiO2 hydrogel nanocomposite using different days (1, 4, and 7) of activity.
nanoparticles can cause the H-PVA hydrogel to expand, thereby expanding the pores and free spaces in the H-PVA hydrogel, which would thereby absorb more water [41].

3.5. Antibacterial studies
Figure 5(A) shows the antibacterial activity of the H-PVA hydrogel and H-PVA@TiO₂ bandages against Gram-positive (S. aureus) and Gram-negative (E. coli) bacteria using the colony formation technique. The results indicated the H-PVA@TiO₂ nanocomposite hydrogel had better activity towards Gram-positive and Gram-negative bacteria. As shown by the colony formation data, the as-fabricated H-PVA@TiO₂ bandages exhibited better antibacterial properties on Gram-positive and Gram-negative bacteria than the H-PVA hydrogel. The antibacterial activity of H-PVA@TiO₂ is due to the presence of TiO₂, which can attack the bacterial cell wall and cause the leakage of cell contents leading to bacterial death [42].

3.6. Biocompatibility studies
The cell viability results as shown in figure 5(B), confirmed that the collagen and H-PVA hydrogel (controls) exhibited no incubation after days 1, 4, and 7 with human dermal fibroblast (HFF2) cells. The as-prepared H-PVA@TiO₂ bandages showed 82% viability after the first day of cell culture. The viability of the H-PVA@TiO₂ bandages increased to ~86% and ~96% after 4 and 7 days of incubation, respectively. Furthermore, the lower cell viability on the first day was due to the interaction of TiO₂ nanoparticles with the fibroblast cells. After the first day, the remaining cells began to proliferate, thereby improving viability [43–46].

3.7. Evaluation of animal model
H-PVA@TiO₂ bandages based on heparin-polyvinylalcohol containing TiO₂ nanoparticles, which have excellent mechanical, antibacterial, and cell proliferation properties, provide extensive therapeutic benefits for wound healing applications [42]. An in vivo study with Kunming mice showed an improved healing ability of the as-prepared H-PVA hydrogel and H-PVA@TiO₂ bandages, which was measured and photographed periodically after day 3, 7, 11, and 14, and the percentage wound closure was calculated by histopathology analysis. Figure 6 presents wound imaging photos at different periods of using the H-PVA hydrogel and H-PVA@TiO₂ bandages. Injuries in the mice were observed once every seven days for the progress of healing. A significant decrease in the wound area was observed in the treated group with the H-PVA@TiO₂ bandage, wherein it decreased on day 7, and its removal, resulting in tissue loss, was achieved on day 14. Wounds treated with the as-prepared H-PVA@TiO₂ bandage demonstrated better healing compared to the control. These results indicated that the incorporation of TiO₂ nanoparticles into the H-PVA hydrogel significantly improved the healing potential. In contrast, the wound closure rate for the H-PVA@TiO₂ bandage was higher than that with H-PVA hydrogel. According to our results, the presence of TiO₂ had better wound healing properties compared to the control [47–49].
3.8. Histological evaluation

Histological analysis is a powerful method to observe the progress in healing and tissue regeneration of wounds. The histological analysis focused on the healing ability of injured mice tissues due to the influence of hematoxylin and eosin (H&E) staining on the H-PVA hydrogel (control) and H-PVA@TiO$_2$ (figure 7). The H-PVA hydrogel and H-PVA@TiO$_2$ showed excellent healing after day 11 and 14, in contrast to the bare wound. In figure 7, the histological sections indicated compact keratinocytes in the epidermis on wounds coated with H-PVA hydrogel and H-PVA@TiO$_2$, compared to the bare wound. Besides, the existence of TiO$_2$ nanoparticles improved the healing rate of H-PVA@TiO$_2$ coated wounds, which was evident from the histological micrographs. The biocompatibility and anticoagulant properties of TiO$_2$ nanoparticles make it an excellent candidate for wound healing, as seen in vitro and in vivo studies. Conversely, absolute regrowth of new subcutaneous tissues was quantitated by segment light microscopy. The degree of wound closure was estimated at macroscopically [50–52]. The results (figure 7) suggested that the H-PVA@TiO$_2$ nanocomposite treatment promotes significant healing through the migration of fibroblasts and appropriate development of epithelial cells and the restoration of blood flow via training of new blood vessels. In our attempt to develop a tissue dressing technique, we created an H-PVA@TiO$_2$ bandage material based on H-PVA hydrogel conjugated with TiO$_2$ nanoparticles, which was tested for the first time for the wound healing application, to the best of our knowledge.

4. Conclusions

We have developed a heparin-polyvinylalcohol@TiO$_2$ nanocomposite bandage (H-PVA@TiO$_2$) by the freeze-drying method for wound healing applications. The prepared H-PVA and H-PVA@TiO$_2$ bandages were flexible. The H-PVA@TiO$_2$ bandage displayed a high porosity that was encouraging for the augmentation of fibroblasts...
cells, which is advantageous for a wound dressing. The porous nature of the H-PVA@TiO2 bandages was not altered significantly with the addition of TiO2. The existence of TiO2 nanoparticles in the H-PVA hydrogel was verified via XRD spectra and their interface with hydrogel was studied with FTIR. The microporous structure of the bandage improved the rate of swelling and controlled the degradation, which would help absorb exudates and increase the hemostatic potential of the wound surface. The TEM results showed that the TiO2 nanoparticles have an average size of approximately 100 nm. The developed H-PVA@TiO2 nanocomposite was well characterized and tested for its mechanical properties (tensile strength, elongation rate, tensile modulus) and in vivo wound healing capacities. H-PVA@TiO2 nanocomposites showed good antimicrobial activity towards Gram-positive and Gram-negative bacteria. In vitro biocompatibility studies have shown that H-PVA@TiO2 dressings demonstrate enhanced cell proliferation and penetration. Excellent findings from the animal study of Kunming mice reported that H-PVA@TiO2 bandage triggers 95 percent recovery of damaged depth fragments within 14 days. Based on these results, the prepared H-PVA@TiO2 nanomaterials could be further used in medical fields.

Data availability statement

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

Conflict of the interest

None
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