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Nintedanib alleviates polypropylene mesh-induced adhesion in rabbit ventral herniorrhaphy

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Abstract

BACKGROUND: Nintedanib (previously known as BBIF 1120) was approved by the United States Food and Drug Administration and European Medical Agency to treat idiopathic lung fibrosis in the year 2014 and 2015, respectively. It is now gaining interest for its anti-fibrotic activity in other organs and disease conditions. Although a surgical mesh is used as a mainstay therapy for herniorrhaphy, postoperative peritoneal adhesion with a polypropylene mesh is a significant drawback. This study aims to assess the efficacy of nintedanib in preventing postoperative adhesion incited with a polypropylene mesh in a rabbit model of ventral hernia.

MATERIALS AND METHODS: Ventral hernia was induced surgically in ten adult healthy New Zealand White rabbits of either sex. Hernioplasty was performed with a polypropylene mesh, and the rabbits were randomly allocated into two groups to receive either oral 1 mL sterile water or 100 mg nintedanib in 1 mL of sterile water for 7 days. The adhesion of the implanted mesh with the intra-abdominal organs was assessed clinically, by histological and ultrastructural studies with scanning electron microscopy (SEM) at 30 days postoperatively.

RESULTS: All rabbits were clinically healthy for 30 days post-surgery with no complication at the site of surgery. The incidence of peritoneal adhesion and tenacity was less in the nintedanib group versus the control group ($P = 0.00105$). Histopathological and SEM evaluations also indicated less fibrosis and adhesion in the nintedanib-treated group versus control.

CONCLUSION: Our results show successful prevention of mesh-associated adhesion with nintedanib, but further studies on the mechanistic pathway, pharmacokinetics, dose standardization, and evaluation of systemic side effects are warranted.

Keywords:

Adhesion, hernia, nintedanib, polypropylene mesh, prevention

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Introduction

In medical sciences, hernia repair using a prosthetic mesh remains the popular and preferred method owing to the lower recurrence rate.[1,2]

Despite the advantages of a polypropylene mesh as a prosthetic material for hernia repair, a major drawback is the inflammatory response it incites, which triggers the adhesion formation.[3] Other complications associated are infections and conditions such as intestinal obstruction and enterocutaneous fistulas.[4-8]

A key factor in the formation of peritoneal adhesion is attributed to myofibroblasts,[9] which results from the mesothelial-to-mesenchymal transition.[10] Pro-fibrotic and pro-inflammatory mediators secreted by inflammatory cells, that is, fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factors (PDGF), potentiate extracellular matrix synthesis by myofibroblasts along with its activation and proliferation.[11,12]

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Nintedanib, a multitarget tyrosine kinase inhibitor, is a Food and Drug Administration (FDA)-approved drug for lung fibrosis.

A recent study has reported its activity in preventing mesothelial-to-mesenchymal transition.[13] Considering adhesion is an alarming complication with use of the polypropylene mesh, we selected this small-molecule drug for evaluating its efficacy in preventing peritoneal adhesion associated with mesh implantation in a rabbit model of ventral hernia.

Materials and Methods

Systemic use of nintedanib for prevention of adhesion following hernia repair with a polypropylene mesh in rabbit

All studies were conducted with prior permission of the Institutional Animal Ethics committee. Vide approval no. 763/GO/Re/SL/03/CPCSEA/11/2021-2022.

The study was conducted on 10 adult healthy New Zealand White rabbits of either sex weighing around 2 kg. They were acclimatized for 1 week after procurement and were maintained under iso-managemental conditions with 12-h light and dark cycle.

Evaluation of nintedanib as an anti-fibrotic agent in repair of ventral hernia using a polypropylene mesh

Anesthesia was induced with a combination of ketamine hydrochloride at 35 mg/kg and xylazine hydrochloride at 5 mg/kg. The operative site was aseptically prepared by epilation of the fur, followed by antiseptic painting with povidone iodine and covering with a sterile drape. A 1.3-cm midline incision was made, and by dissection of the muscle, the peritoneal cavity was entered through the linea alba at a distance of 3 cm caudal to the xyphoid process. The abdominal muscles and peritoneum of 1 cm × 5 cm dimension were removed, and the defect was repaired using the 1.5 cm × 1 cm polypropylene mesh placed as an underlay implant, by securing it to the abdominal muscles using continuous sutures with 4-0 polypropylene sutures. After the fixation of the polypropylene mesh, the muscle and skin were closed with continuous 4-0 polyglactin 910 sutures [Figure 1].

Rabbits ($n = 5$) were orally administered with 100 mg of nintedanib (Nintena100, Sun Pharmaceutical Ind. Ltd., Gujarat, India) in 1 mL of sterile water once daily for 7 days, and in another set, the operated rabbits (5) were administered with 1 mL of sterile water once daily as the control treatment for 7 days.

Post-operative management was followed by antibiotics (Inj. cefotaxim) at 25 mg/kg, i.m. 12-hourly and anti-inflammatory (meloxicam injection) at 0.2 mg/kg, s.c. once daily were administered for consecutive 5 days and 3 days, respectively. Post-operative dressings were conducted on the third day, fifth day, and seventh day after surgery.

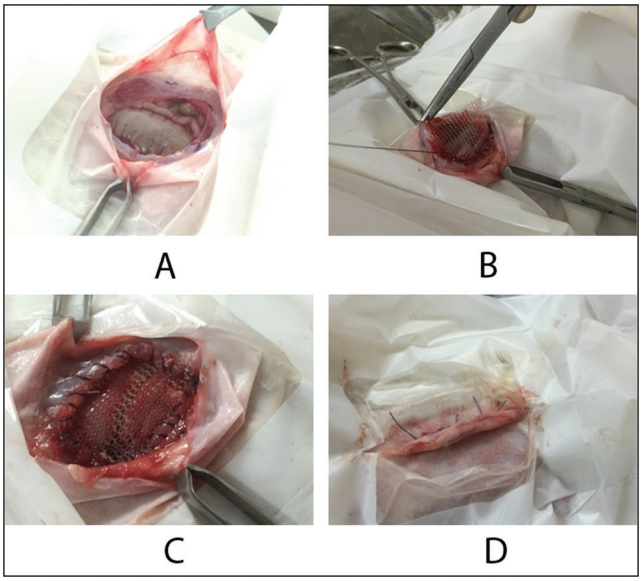

Figure 1: Representative pictures show the steps followed for underlay implantation of the polypropylene mesh within the abdominal cavity. (A) A full-thickness defect was surgically created in the ventral abdomen of the rabbit. (B) The mesh was implanted as an underlay within the peritoneal cavity. (C) The mesh was secured to the abdominal wall using continuous sutures 4-0 polyglactin 910. (D) The skin and muscle were repaired using absorbable sutures

Evaluation of adhesion of the implanted mesh with the intra-abdominal organs

One month after implantation, the animals were euthanized with an overdose of anesthesia (ketamine hydrochloride > 200 mg/kg), and the skin and muscles around the site of implantation were dissected with the anterior part intact, the skin muscle flap was slowly lifted, and the bowel muscle adhesion was evaluated and graded.[14] In brief, gradation and scoring were done as 0 = no adhesion, 1 = thin and easily separated adhesion, 2 = narrow-range weak adhesion, but able to withstand mild traction, 3 = adhesion present in two locations or fairly firm adhesion, and 4 = adhesion present in three or more locations.

The mesh muscle implant was harvested and preserved in either 2.5% glutaraldehyde or 10% formalin in sterile containers for scanning electron microscopy (SEM) and histopathological examination.

Histopathology

The standard protocol was followed for histopathology and staining. In brief, the tissues were fixed in 10% formalin, cleared in xylene, dehydrated in graded alcohol, and embedded in paraffin. Tissue

sections of 5 microns were prepared and stained with hematoxylin and eosin and observed under a light microscope.

SEM

The tissue from the operation site was preserved in 2.5% glutaraldehyde. Then, the tissues were dehydrated gradually by incubation in graded alcohol, that is, in 70% alcohol for 30 min, 80% alcohol for 30 min, 90% alcohol for 30 min, and finally in absolute alcohol. Tissues were subjected to critical point drying and followed by gold spraying and observed under the scanning electron microscope.

Statistical methods

Data are expressed as either mean ± SD or mean ± SE, as indicated. Comparison between groups was performed by Students *t* test.

Results

Adhesion prevention using systemic nintedanib

There was significant reduction in the adhesion score in the nintedanib-treated animals versus the controls, that is, sterile water-treated animals, $P = 0.00105$. Strong adhesions in multiples sites were recorded in the control animals. In the nintedanib-treated rabbits, adhesion severity was considerably reduced, and complete absence of adhesion was recorded in three out of five animals [Table 1] and [Figure 2].

Table 1: Adhesion scoring for nintedanib-treated animals

Animal no.	Treated	Control
1	0	4
2	1	4
3	2	4
4	0	4
5	0	4

Adhesion scoring for nintedanib-treated animals: Treated—Mean = 0.6; SD = 0.89. Control—Mean = 4; SD = 0
$P = 0.000028$ (significant)

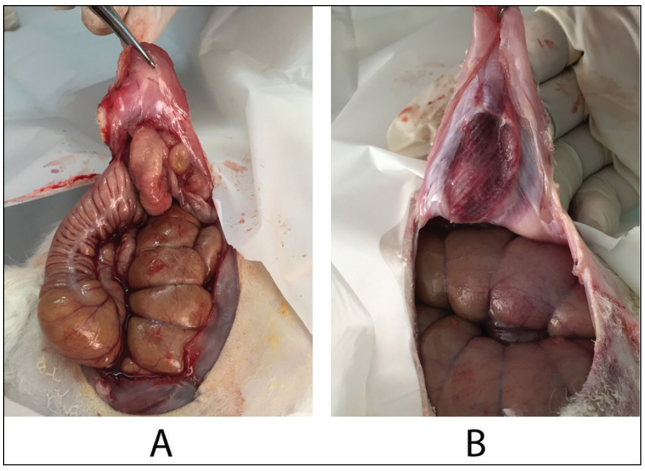

Figure 2: Representative picture of the mesh-implanted site shown (A) Severe adhesion in multiple sites was observed in the control animal. (B) Complete absence of adhesion in systemic nintedanib-treated animal

Histopathological findings of tissue–mesh explants

Histopathological studies were conducted to study the tissue adhesion studies with and without drug therapy for prevention of adhesion with polypropylene mesh implantation.

There was appreciable prevention of tissue adhesion in nintedanib-treated animals [Figure 3].

Appropriate tissue integration of mesh is imperative for successful hernia repair, and we observed comparable tissue integration of the mesh with the abdominal muscle and peritoneum in the tissue sections from nintedanib-treated and untreated tissues [Figure 4].

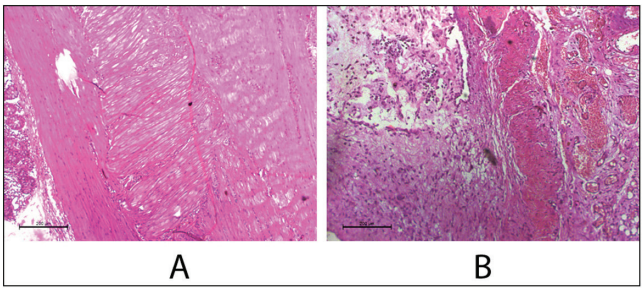

Figure 3: (A) Representative micropictograph of tissue sections from the mesh-implanted sites show noticeable adhesion of the intestinal tissue with the mesothelium of the peritoneum in control. (B) The peritoneal layer of the treated tissues was free of adhesion

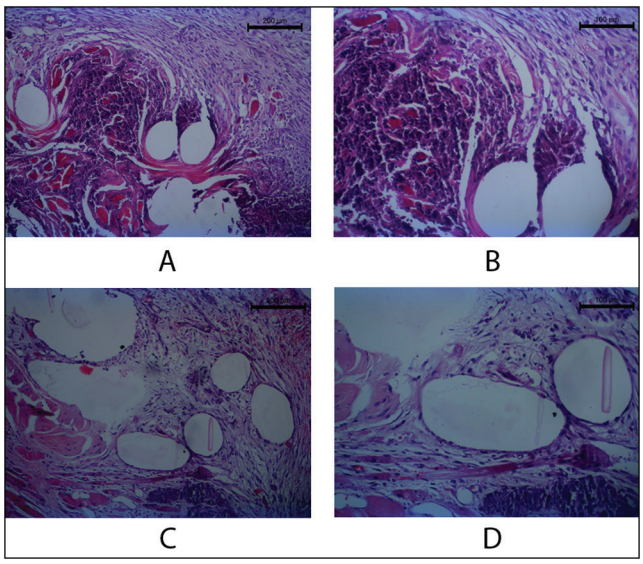

Figure 4: Representative micropictographs of tissue sections from the mesh-implanted sites show comparable tissue integration of the mesh with the abdominal muscle and peritoneal tissues in the untreated A (10×) and B (20×) and nintedanib-treated C (10×) and D (20×) group

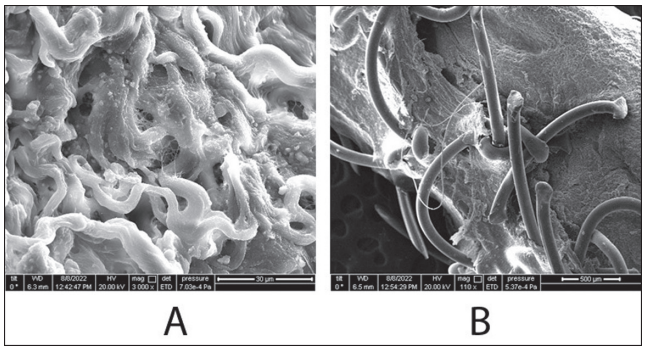

Figure 5: Micro pictographs of scanning electron microscopy shown. (A) The section from the control animal shows frank adhesion of the peritoneal tissue with the mesh. (B) Muscle and mesh without any adhesion in nintedanib-treated tissue

SEM of tissue explants with mesh

Ultrastructural studies of the tissues from treated and untreated mesh-implanted animals were evaluated with SEM. The tissues show the absence of adhesion in the treated animals with well-formed mesothelial tissues. There was distinct presence of adhesion in the control tissues [Figure 5].

Discussion

In the last decade, surgeons have adopted the benefits of the tremendous technological advancements, that is, robotic devices and laser ablation. However, challenges that still persist even with those involved in cutting edge research are strategies to prevent healing surfaces from sticking (adhesion) and enhancing the healing of operated tissues.[15]

The use of a prosthetic mesh is routine for correction of hernias. Adhesion with the polypropylene mesh is highest among the synthetic meshes in clinical use, which is owing to the intense inflammatory response incited by the material; however, its advantages are ease of handling and low price.[3,16] However, considering the major disadvantages encountered post implantation, that is, tissue adhesion and infection, two pertinent approaches identified to prevent mesh-associated adhesion are use of physical barriers or therapeutic modalities, which include fibrinolytic agents and anti-fibrotic and anti-inflammatory drugs.

Given the understanding of the pathophysiology of adhesion, we conceptualized the prevention of mesothelial-to-mesenchymal transition, and the associated pro-fibrotic events leading to post-surgical adhesion with polypropylene mesh may be a pertinent approach to address the unmet clinical need. We therefore selected nintedanib for adhesion prevention. It is an FDA-approved anti-fibrotic drug that renders its action by triple tyrosine kinase inhibition of PDGF, FGF, and VEGF. All of these factors contribute significantly to mesothelial–mesenchymal transition and peritoneal adhesion.[10]

Our study shows significant prevention of mesh and peritoneal adhesion following oral administration of nintedanib, and the histopathological and scanning electron microscopic reports also support the clinical findings. Similar results have been demonstrated by Fu *et al.*[17] The mentioned study was conducted to evaluate adhesion prevention with peritoneal ischemic buttons in a rat model. It was also interesting to note the comparable tissue integration of the mesh in nintedanib-treated and untreated animals, which implies that the drug does not hinder the repair process.

Conclusion

To the best of our knowledge, use of nintedanib to prevent polypropylene mesh-induced adhesion has not been reported earlier, and the results of our study may pave the way for a new therapeutic approach. However, further studies on the pharmacokinetics of the drug, mechanism of activity, and standardization of dose are warranted.

Author contributions

Sourav Mathur: performed experiment and data collection. Indrani Hazra: conceptualization. Aditya Konar: conceptualization and manuscript editing. Sarbani Hazra: conceptualization, data analysis, manuscript drafting, and review and correction.

Ethical policy and institutional review board statement

The study was approved by the Institutional Animal Ethics committee (IAEC), West Bengal University of Animal and Fishery Sciences. Kolkata. India (Approval no. 763/GO/Re/SL/03/CPCSEA/11/2021-2022, dated on April 12th, 2022).

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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