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Preclinical Evaluation Of Acute And Chronic Systemic Toxicity Of A Novel Composite-Coated Mesh Implant For Minimally Invasive Hernioplasty

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Abstract: Background. Synthetic mesh implants are widely used in minimally invasive hernioplasty; however, their systemic safety remains a critical concern, particularly when modified with composite coatings. According to international standards, preclinical evaluation of acute and chronic toxicity is mandatory prior to clinical translation. Objective. To assess the acute and chronic systemic toxicity of a novel composite-coated mesh implant in accordance with ISO 10993-11. Methods. A preclinical in vivo study was performed on laboratory rats divided into acute (7 days) and chronic (1 and 3 months) observation groups (n = 30 per group). A 1 × 1 cm fragment of the composite-coated mesh was implanted onto the diaphragmatic surface of the liver. Clinical condition, body weight dynamics, relative organ mass coefficients, hematological indices, serum biochemical parameters, and histopathological changes were evaluated and compared with control groups. Results. No mortality or signs of

systemic toxicity were observed throughout the study. Body weight gain remained within physiological ranges in all groups. Relative organ mass coefficients did not differ significantly from controls ($p > 0.05$), except for a transient increase in liver mass at day 7 without histopathological abnormalities. Hematological and biochemical parameters remained within reference limits at all time points ($p > 0.05$). Histological examination revealed no degenerative or necrotic changes in major organs. Conclusion. The composite-coated mesh implant did not induce acute or chronic systemic toxicity in rats and can be classified as a low-toxicity medical device. These findings support its preclinical safety and justify further experimental and clinical investigation.

Keywords: Composite mesh, biocompatibility, systemic toxicity, experimental model, tissue response, minimally invasive surgery.

Introduction: The use of synthetic mesh implants has become a standard approach in modern minimally invasive hernioplasty due to their mechanical strength, availability, and favorable long-term outcomes. Nevertheless, postoperative complications such as chronic inflammation, fibrosis, infection, and impaired tissue integration remain clinically significant and may compromise surgical success. These adverse effects are often associated with the interaction between implanted materials and the host biological environment [1-7,10-12].

Recent advances in biomaterials research have focused on modifying conventional meshes with composite coatings in order to improve biocompatibility, reduce inflammatory reactions, and provide additional functional properties such as hemostatic or antimicrobial activity. However, any modification of implant surfaces may alter not only local tissue responses but also systemic biological effects. Therefore, rigorous preclinical safety evaluation is required before clinical application [6,9,10,12].

According to international regulatory standards, particularly ISO 10993-11, assessment of acute and chronic systemic toxicity is a mandatory component of biocompatibility testing for implantable medical devices. These evaluations are essential to exclude potential toxic effects on major organs, metabolic systems, and hematological parameters following short- and long-term exposure [8,9].

Despite the growing number of composite-coated implants proposed for surgical use, data regarding their systemic safety remain limited. In this context, the present study was designed to provide a comprehensive preclinical assessment of the acute and chronic toxicity of a novel composite-coated mesh implant using an in vivo rat model.

The objective of this study was to evaluate the systemic effects of the composite-coated mesh by analyzing clinical condition, body weight dynamics, relative organ mass coefficients, hematological and biochemical parameters, and histopathological changes in accordance with ISO 10993-11 requirements.

METHODS

Study Design. A preclinical in vivo study was conducted to evaluate the acute and chronic systemic toxicity of a novel composite-coated mesh implant in accordance with the requirements of ISO 10993-11. The experimental protocol included an acute toxicity assessment (7 days) and a chronic toxicity assessment (1 and 3 months).

Experimental Model and Ethical Approval. The study was conducted at the Department of Experimental Surgery and the Laboratory of Pathomorphology of the Republican Specialized Scientific and Practical Medical Center of Surgery named after Academician V. V. Vakhidov (Tashkent, Uzbekistan).

The experiments were performed on male outbred white rats (n = 30 per group) weighing 210-250 g. Animals were housed under standard vivarium conditions with a natural light-dark cycle, ambient temperature of 22 ± 2 °C, and free access to food and water.

All procedures were carried out in strict accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and were approved by the local ethics committee of the institution.

Implant Description. The tested medical device was a novel composite-coated synthetic mesh implant designed for minimally invasive hernioplasty. The coating was applied to improve biocompatibility and functional performance of the mesh. Sterile, non-coated mesh fragments served as controls.

Surgical Procedure. Under general anesthesia, a 1×1 cm fragment of the composite-coated mesh was implanted onto the diaphragmatic surface of the liver through a mini-laparotomy. The control group received non-coated mesh implants of the same size. After implantation, the abdominal wall was sutured in layers.

Observation Periods. Animals were monitored for:

- Acute toxicity: 7 days
- Chronic toxicity: 1 month and 3 months

Clinical Assessment. Throughout the observation period, animals were evaluated daily for general condition, behavior, food and water intake, and signs of distress or toxicity. Body weight was recorded weekly.

Organ Coefficient Analysis. At each time point, animals were euthanized, and the liver, kidneys, heart, lungs, and spleen were harvested and weighed. Relative organ mass coefficients were calculated as the ratio of organ weight to body weight.

Hematological and Biochemical Analysis. Blood samples were collected for complete blood count and serum biochemical analysis, including liver and kidney function markers. All values were compared with reference ranges and control groups.

Histopathological Examination. Major organs were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned (4-5 µm), and stained with hematoxylin and eosin. Histological evaluation was performed under light microscopy.

Statistical Analysis. Data are presented as mean ± standard deviation. Statistical analysis was performed using Student's t-test. Differences were considered significant at $p < 0.05$.

RESULTS

General Clinical Observations. Throughout the entire observation period, no significant changes in the clinical condition or behavior of the experimental animals were recorded. No delayed mortality was observed. Food and water intake in the experimental groups did not differ significantly from the control group. Body weight dynamics remained positive in all groups.

Compared with intact animals, rats implanted with the composite-coated mesh did not demonstrate statistically significant differences in the rate of body weight gain ($p > 0.05$), indicating the absence of systemic toxicity (Table 1, Figure 1).

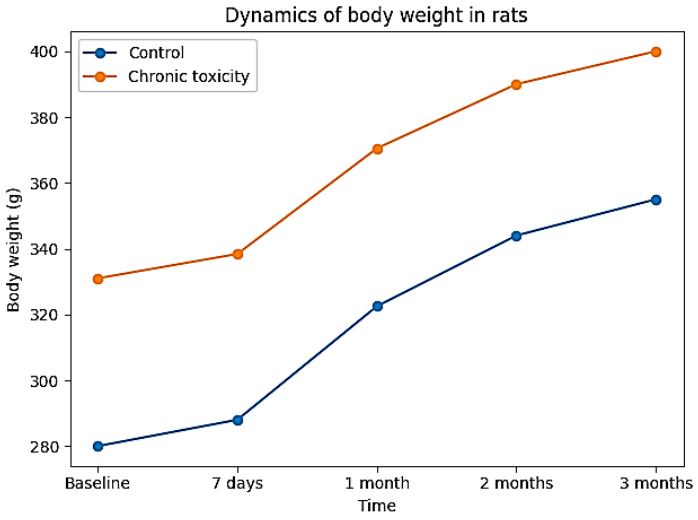

Figure 1. Dynamics of body weight in rats after implantation.

Table 1.
Dynamics of Body Weight in Rats after Implantation of Composite-Coated Mesh

Group	Baseline (g)	7 days	1 month	2 months	3 months	Weight gain (%)
Control	280 ± 0.05	288 ± 0.05	322.5 ± 0.05	344 ± 0.05	355 ± 0.05	+26.7
Acute toxicity	330 ± 0.05	335.4 ± 0.05	—	—	—	+1.5
Chronic toxicity	331 ± 0.05	338.4 ± 0.05	370.5 ± 0.05	390 ± 0.05	400 ± 0.05	+20.8

$p < 0.05$ (within groups)

Organ Coefficient Analysis. The organ mass coefficient (OMC), calculated as the percentage ratio of organ mass to body mass, is widely used in toxicological studies to evaluate internal organ status.

Implantation of the mesh did not cause statistically significant changes in kidney and spleen coefficients compared with controls. However, a moderate increase in the liver coefficient was observed in the experimental groups, reflecting adaptive metabolic changes rather than toxic injury (Table 2).

Table 2.
Organ Mass Coefficients after Implantation

Organ	Control	7 days	1 month	2 months	3 months
Kidneys	2.3 ± 0.05	2.5 ± 0.05	2.3 ± 0.05	1.9 ± 0.05	2.6 ± 0.05
Spleen	0.9 ± 0.05	1.16 ± 0.05	1.16 ± 0.05	0.8 ± 0.05	1.3 ± 0.05
Liver	9.0 ± 0.05	10.0 ± 0.05	11.4 ± 0.05	9.0 ± 0.05	12.8 ± 0.05

$p < 0.05$

Hematological Findings. No statistically significant differences were observed between experimental and control groups in erythrocytes, hemoglobin, leukocytes, lymphocytes, monocytes, or eosinophils ($p > 0.05$). All parameters remained within physiological limits (Table 3).

Table 3.
Complete Blood Count

Parameter	Control	Acute tox.	1 month	2 months	3 months
Hemoglobin (g/L)	156 ± 31.5	146.4 ± 24.5	136.6 ± 65.9	110 ± 13.9	133 ± 15.5
RBC ($\times 10^{12}$/L)	8.2 ± 0.57	7.7 ± 0.61	7.76 ± 0.46	7.0 ± 0.59	7.8 ± 0.55
Platelets ($\times 10^{9}$/L)	826 ± 32.1	945.2 ± 27.8	750 ± 30.5	806 ± 35.2	961 ± 32.5
WBC ($\times 10^{9}$/L)	5.4 ± 0.55	7.8 ± 0.64	9.5 ± 0.49	7.35 ± 0.43	7.2 ± 0.5
Band neutrophils (%)	1.0 ± 0.2	4.8 ± 0.35	11.0 ± 0.45	14.0 ± 0.68	4.6 ± 0.3
Segmented neutrophils (%)	15.0 ± 0.2	18.2 ± 0.36	19.6 ± 0.4	22.5 ± 0.65	12.3 ± 0.15
Lymphocytes (%)	80.0 ± 0.69	69.8 ± 0.55	63.4 ± 0.5	63.4 ± 0.5	80.0 ± 0.69

$p > 0.05$

Biochemical Analysis. Serum biochemical parameters showed no clinically significant deviations (Table 4). Enzyme activity (ALT, AST), bilirubin, cholesterol, glucose, and total protein remained within physiological ranges.

Table 4.
Serum Biochemical Parameters

Parameter	Control	Acute	1 month	2 months	3 months
ALT (U/L)	43.5 ± 2	53.6 ± 2.8	52.8 ± 2.5	71.5 ± 3.3	79 ± 3.6
AST (U/L)	70 ± 4.3	61 ± 3.5	24 ± 1.5	24.6 ± 1.56	26.2 ± 1.8
Cholesterol (mmol/L)	1.4 ± 0.14	1.4 ± 0.14	1.6 ± 0.2	1.5 ± 0.18	1.4 ± 0.14
Glucose (mmol/L)	4.4 ± 0.4	8.6 ± 0.66	6.6 ± 0.5	6.2 ± 0.49	5.9 ± 0.45

Total protein (g/L)	77.5 ± 1.46	65.9 ± 1.25	70.7 ± 1.34	79 ± 1.49	76.6 ± 1.45
Total bilirubin (μmol/L)	6.0 ± 0.5	7.3 ± 0.66	6.4 ± 0.52	10 ± 0.85	6.3 ± 0.48

$p > 0.05$

DISCUSSION

The present study provides comprehensive preclinical evidence that the novel composite-coated mesh implant does not induce acute or chronic systemic toxicity and demonstrates a high level of biocompatibility. According to ISO 10993-11, systemic toxicity is defined by the presence of mortality, weight loss, organ dysfunction, or clinically relevant hematological and biochemical abnormalities. None of these criteria were observed in the current experiment, confirming the systemic safety of the tested implant.

Body weight dynamics are considered a sensitive indicator of systemic toxicity in experimental models. In our study, weight gain in both acute and chronic experimental groups was comparable to the intact control group, indicating preserved metabolic homeostasis. Similar findings have been reported for modern biocompatible meshes and composite materials used in abdominal surgery, where stable weight gain reflects minimal systemic stress and good tolerance of the implant [6,9].

The moderate increase in liver mass coefficient observed at early time points likely reflects a physiological metabolic adaptation rather than toxic injury. This interpretation is supported by the absence of histopathological abnormalities and by stable ALT and AST levels. Transient hepatic enlargement has been described in experimental models following implantation of biocompatible polymers and is commonly associated with increased protein synthesis and detoxification activity rather than hepatotoxicity [7,10].

Hematological parameters represent a key indicator of systemic immune activation. In the present study, erythrocyte, hemoglobin, platelet, and lymphocyte levels remained within physiological ranges. The transient leukocytosis and neutrophilia observed during the early and mid-term periods correspond to a normal inflammatory response to surgical trauma and foreign material implantation. Similar temporary changes have been reported in preclinical studies of mesh implants and generally resolve as tissue integration progresses [6,7].

Importantly, normalization of leukocyte profiles by month 3 indicates the absence of chronic immune stimulation, which is a known risk factor for fibrosis, biofilm formation, and implant rejection [7].

The stability of kidney and spleen mass coefficients, together with normal biochemical parameters, demonstrates that the composite-coated mesh does not exert nephrotoxic or hematotoxic effects. These findings are critical, as systemic toxicity is one of the major barriers to clinical translation of modified implantable materials [9].

Recent studies have emphasized that surface-modified and composite meshes may potentially alter systemic immune responses if not properly engineered. However, when biocompatible coatings are used, systemic effects remain minimal while local integration improves [6,9,10,12].

Postoperative complications after hernioplasty, including chronic inflammation, fibrosis, and infection, are often related to poor biocompatibility and bacterial adhesion on implant surfaces [1-3,7,10]. Composite coatings have been proposed as a strategy to reduce these risks by modifying the implant-tissue interface. Our findings are consistent with previous experimental studies demonstrating that optimized mesh coatings reduce inflammatory responses and improve tissue remodeling without inducing systemic toxicity [2,5,9].

Furthermore, bacterial biofilm formation on mesh implants has been identified as a major contributor to surgical site infections and chronic complications [7,12]. Although the present study focused on systemic safety, the absence of prolonged inflammatory activation supports the potential of composite coatings to minimize infection-related risks, as suggested by in vitro and in vivo studies [3,7,10].

This study was limited to systemic toxicity assessment and did not directly quantify bacterial load or local cytokine expression. Future investigations should incorporate molecular and microbiological analyses to further elucidate the immunomodulatory mechanisms of composite coatings. Additionally, long-term functional studies and clinical trials are required to confirm translational relevance.

Taken together, the present data indicate that the composite-coated mesh implant demonstrates excellent systemic biocompatibility and does not induce acute or chronic toxicity. These findings support its further development as a safe and effective material for minimally invasive hernioplasty.

CONCLUSIONS

1. The composite-coated mesh implant demonstrated high systemic biocompatibility and did not induce acute or chronic toxicity in experimental animals, as confirmed by stable body weight dynamics, absence of mortality, and preserved behavioral activity throughout the observation period.
2. Organ mass coefficients for the kidneys and spleen remained within physiological limits, while the transient increase in liver mass coefficient was not accompanied by pathological biochemical changes, indicating adaptive metabolic responses rather than toxic injury.
3. Hematological parameters remained within reference ranges in both acute and chronic experimental groups, with only temporary and reversible inflammatory shifts, confirming the absence of sustained immune activation or hematotoxic effects.
4. Biochemical analysis of blood serum showed no clinically significant deviations in ALT, AST, glucose, cholesterol, total protein, or bilirubin levels, demonstrating preserved hepatic and metabolic function.
5. The obtained results confirm that the tested composite coating does not impair systemic homeostasis and ensures safe interaction between the implant and biological tissues.
6. The combined use of synthetic mesh implants with composite coatings represents a promising and safe strategy for minimizing postoperative complications and improving outcomes in minimally invasive abdominal surgery.

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