Abstract. – OBJECTIVE: To design a new controlled-release MMC-PLA film and explore whether and how this film could prevent epidural scar hyperplasia and adhesion in a post-laminectomy rat model.

MATERIALS AND METHODS: All procedures were performed under the approval and supervision of the Institutional Animal Care and Use Committee (IACUC) of Nanjing Medical University. A total of 120 Sprague-Dawley (SD) rats were randomly placed into four groups after laminectomy (each group=30 rats). In Group I, the laminectomy area was flushed with saline as a control; in Group II, 25 mg of PLA film was applied to the dura mater in the laminectomy area; in Group III, a cotton pad soaked with 0.01% MMC solution was kept on the laminectomy area; and in Group IV, 25 mg of PLA film containing 0.01% MMC was implanted on the laminectomy area. Magnetic resonance imaging (MRI), hematoxylin-eosin (HE) staining and Masson staining were used to evaluate scar adhesion and collagen deposition one month after the operation. Autophagy-related proteins, including autophagy-related gene 5 (ATG5), beclin 1, light chain-3B-2/1 (LC3B-2/1) and protein 53 (p53), were detected by Western blotting. A microRNA microarray analysis was performed to screen for scar tissue miRNAs, especially those associated with autophagy, and changes in expression were confirmed by reverse transcription-polymerase chain reaction (RT-PCR).

RESULTS: A total of 112 rats recovered uneventfully from the surgery. MRI showed that the scar adhesion and scar area of the MMC-PLA group were significantly reduced compared with those of the PLA, MMC, and saline groups. Accordingly, scar adhesion and the deposition of collagen in the rats treated with MMC-PLA were also significantly reduced, as indicated by HE and Masson staining. In the scar tissue, the levels of autophagy-related proteins (ATG5, beclin 1, LC3B-2/1 and p53) were significantly elevated in the MMC-PLA group. Additionally, in the MMC-PLA group, the expression levels of miR-34a, miR-146a and miR-200 were significantly increased, while the levels of miR-16, miR-221 and miR-378a were significantly decreased.

CONCLUSIONS: The controlled-release MMC-PLA film could alleviate epidural scar hyperplasia after laminectomy; this outcome might be associated with increased autophagy and altered expression of miRNAs in the scar tissue.

Key Words: Spine, Laminectomy, Polylactic acid film, Mitomycin C, Autophagy, miRNA.

Introduction

Laminectomy is one of the most commonly used surgical methods of vertebral canal decompression and can effectively reduce nerve root and spinal cord compression. However, failed back syndrome, with continued or recurrent pain and nerve dysfunction, sometimes occurs post-laminectomy. The reasons for failed back syndrome are diverse. However, one likely cause is that many epidural fibroblasts extend into the vertebral canal, produce an extracellular matrix and adhere to the epidural and nerve roots, eventually leading to recurrent pain and nerve dysfunction. Although the symptoms can be alleviated by reoperation, the repeated operation...
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does not work for some patients and may even cause nerve injury\(^5\). Therefore, preventing or reducing postoperative epidural scar formation may decrease the occurrence of spinal stenosis, which would improve the surgical outcomes and quality of life of patients and avoid unnecessary reoperation. Researchers have investigated various methods to prevent epidural fibrosis and inhibit scar hyperplasia, including membranous or biological materials; fluids or semi-fluids; immunotherapy; and topical drug application\(^8\)-\(^11\). Among these methods, the local application of mitomycin C (MMC) effectively inhibits epidural scar hyperplasia, and autophagy was observed in MMC-treated apoptotic fibroblasts\(^12\),\(^13\). However, MMC cannot physically block the adhesion of the surrounding tissue to the epidural and nerve roots\(^4\). Polylactic acid (PLA) film is more biocompatible and has a physical barrier function, but it cannot inhibit the proliferation of fibroblasts in scar tissue\(^15\). In this study, a new PLA film was designed to include a controlled and continuous release of MMC. The controlled-release MMC-PLA film can be used as a physical and chemical barrier to inhibit laminectomy scar hyperplasia in two ways. Experiments in Sprague-Dawley (SD) rats demonstrated that the controlled-release MMC-PLA film could effectively control epidural scar hyperplasia; this outcome may be associated with enhanced fibroblast autophagy and altered miRNA expression in the scar tissue.

**Materials and Methods**

**Animals**

Adult male SD rats (150 ± 20 g) were purchased from Nanjing Medical University Laboratory Animal Center. All animals were maintained in a specific pathogen-free environment at the Nanjing Medical University animal facility. During the experiment, the temperature, light, and humidity were controlled (22 ± 2°C, lights on from 7 AM to 7 PM, 50 ± 5% humidity). Postoperatively, the rats were housed in individual cages, and normal activity was allowed. The rats were observed once a day. The experimental protocols were approved by the Institutional Animal Care and Use Committee (IACUC) of Nanjing Medical University.

**Preparation of MMC-PLA Film and Determination of the Release Rate**

First, two different liquids were prepared. In liquid A, 10 g of PLA was dissolved completely in 90 g of chloroform at room temperature. In Liquid B, 0.1 g of MMC was dissolved in 100 g of Liquid A at room temperature. Then, Liquid B was evaporated and concentrated into a viscous mixture at room temperature. Finally, the viscous mixture was placed on a polytetrafluoroethylene board, and then a film caster with a uniform gap was swiped across the board to obtain a film of uniform thickness. The concentration of MMC-PLA in the film was determined by high-performance liquid chromatography. Briefly, after cutting the MMC-PLA film into pieces, 50 mg was placed into a 50 ml volumetric flask. Then, the film was dissolved in 25% ethanol, and 25% ethanol was added to 50 ml. The mixture was subjected to ultrasonic vibration for 5 minutes and was, then, cooled down to room temperature. After shaking and filtration, the mitomycin C concentration in the filtrate was immediately determined using high-performance liquid chromatography (HPLC). The average concentration of MMC was 0.0098%. To determine the release rate of MMC, the MMC-PLA film was soaked in PBS and stored in a shaker at 37°C and 60 rpm for 30 days. The concentration of MMC released from the film was calculated every 5 days using high-performance liquid chromatography, and the cumulative release of MMC was calculated. All the above materials were sterilized before use.

**Surgical Procedure**

A total of 120 SD rats were randomly placed into four groups after laminectomy (30 rats in each group); then, anesthetized by intraperitoneal injection of 1% pentobarbital sodium solution (4 ml/kg body weight). Antisepsis of the exposed skin was performed with iodophor. The L1 vertebral plate was exposed with a midline skin incision and the dura mater was exposed after removing the spinous process and the L1 vertebral plate with a rongeur. The laminectomy site was treated differently in each of the four groups. In group I (saline group), the laminectomy area was flushed with saline as a control; in group II (PLA group), 25 mg of PLA film was applied on the dura mater in the laminectomy area; in group III (MMC group), a cotton pad soaked with 0.01% MMC solution was kept on the laminectomy area for 5 minutes; and in group IV (MMC-PLA group), 25 mg of PLA film containing 0.01% MMC was implanted on the laminectomy area. All rats were treated by suturing the spinal muscles, fascia,
and skin. Postoperatively, the rats were housed in individual cages, and normal behavior was permitted.

**Magnetic Resonance Imaging**

MRI examinations were carried out immediately after surgery and one-month post-surgery. A total of 32 SD rats (8 rats in each group) were sacrificed using 10% chloral hydrate, then dissected to remove approximately 5 cm of the T11-L3 spine. Magnetic resonance (MR) images were acquired using a Bruker 7.0T Micro-MR imaging system and a Multi-Slice Multi-Echo T2-weighted imaging (MSME T2WI) sequence. The sets of MR images were acquired using the following parameters: time of repetition (TR), 4391 ms; TE, 33.0 ms; layers, 40; thickness, 0.5 mm; and interlayer space, 0; these parameters were followed once, for a total of 10 min 18 s 120 ms per set. The epidural scar area was measured using Image J software.

**Histological Analysis**

One month post-surgery, 32 rats (8 in each group) were randomly selected from the remaining 80 rats. After being anesthetized with 10% chloral hydrate and after intracranial perfusion with 4% paraformaldehyde, the entire spine, including the surrounding muscle tissue, was removed from the L1 segment. The spine tissue was fixed in 4% paraformaldehyde and embedded in paraffin. The sections were stained with hematoxylin-eosin or Masson stain. The extent of scar formation in the four groups was evaluated by morphometric assessment of the scars. The integral optical density (IOD) of the green areas of the sections was analyzed using Image J software.

**Western Blotting**

One month post-surgery, 32 rats (8 in each group) were randomly selected from the remaining 48 rats. After being anesthetized using 10% chloral hydrate and after intracranial perfusion with 4% paraformaldehyde, the entire spine, including the surrounding muscle tissue, was removed from the L1 segment. Two-thirds of the scar tissue from the spine was kept for microRNA microarray analysis and real-time PCR, and the remaining scar tissue was lysed with radioimmunoprecipitation assay (RIPA) buffer (with 1% protease inhibitors and 1% phenylmethylsulfonyl fluoride). The protein content of the supernatant was determined using a bicinchoninic acid (BCA) protein assay kit (Thermo Scientific, Waltham, MA, USA). Equal amounts of lysate (20 μg) were separated using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and blotted onto polyvinylidene difluoride (PVDF) membranes, followed by incubation with antibodies against ATG5 (Abcam, Cambridge, MA, USA, ab108327), beclin 1 (Abcam, ab55878), LC3B (Sigma-Aldrich, St. Louis, MO, USA, L7543), p53 (Abcam, ab26), or GAPDH (Santa Cruz Biotechnology, Santa Cruz, CA, USA, sc-20356) overnight at 4°C. The membranes were then washed with PBST (0.01% Tween-20 in PBS) and incubated with horseradish peroxidase (HRP)-labeled secondary antibodies. The bands were visualized using enhanced chemiluminescence reagents (Perkin Elmer, Waltham, MA, USA) with a 2-min exposure. The density of the immunoreactive bands was measured using Image J software.

**microRNA Microarray Analysis**

Total RNA was extracted from the scar tissue samples from all four groups using TRIzol reagent (Invitrogen Life Technologies, Carlsbad, CA, USA). The RNA isolated from two groups (the MMC-PLA group and the saline group) was then labeled for use with a microRNA Array (Agilent, Santa Clara, CA, USA). Microarray images were acquired using a Genepix 4000B scanner (Axon Instruments, Union City, CA, USA) and were processed and analyzed with Genepix Pro software version 6.0. Real-time PCR was performed to detect related microRNAs.

**Real-Time PCR**

Total RNA was extracted from the scar tissue samples using TRIzol Reagent (Invitrogen Life Technologies) and was reverse transcribed using Superscript II (Invitrogen Life Technologies). Real-time PCR was performed using SYBR green PCR reagent according to the manufacturer’s instructions (Applied Biosystems, Foster City, CA, USA). There were seven primer sets used for amplification (Table I). Quantitative PCR was performed on an Applied Biosystems (ABI, Foster City, CA, USA) Prism 7300 spectrofluorometric thermal cycler (Applied Biosystems) using SYBR Green I as a double-stranded DNA-specific binding dye. The amplification conditions were: 95°C (2 min), then 32 cycles of 95°C (20 s), 57.2°C (30 s), and 72°C (30 s). Quantitative PCR assays were conducted in triplicate for each sample, and analyses were performed using the 2⁻ΔΔCt method.
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Statistical Analysis
All statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). The data are presented as the mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used to analyze the differences between three or more groups, and the Q test was used for two-group comparisons. Differences with \( p < 0.05 \) were considered statistically significant.

Results

The controlled-Release MMC-PLA Film
The release kinetics of MMC were studied in vitro. The MMC-PLA film released MMC over time, with 57% of the MMC released in 15 days and 87% of the MMC released from the film within 30 days (Figure 1).

The Recovery of the Rats and Magnetic Resonance Imaging
After surgery, the recovery of 112 rats (saline group = 28, PLA group = 27, MMC group = 29, MMC-PLA group = 28) was uneventful. Five rats died intraoperatively, and three rats were paralyzed after the operation and were excluded from the study. MRI was an effective tool to evaluate postoperative scar adhesion. In the laminectomy sites of rats treated with saline, the scar tissue and dura mater were covered with severe adhesions, and the scars were the thickest. However, the experimental groups treated with PLA or MMC showed thinner adhesions. The MMC-PLA group showed the thinnest scars and clear spaces between the dura mater and the scar tissue (Figure 2).

Histological Analysis of Epidural Adhesion
All the laminectomy sites in the rats treated with saline or PLA showed epidural scar tissue with many adhesions to the dura mater. However, the rats treated with MMC or MMC-PLA showed sparse epidural scar tissue compared with the rats treated with saline or PLA (Figure 3). Representative histological images of epidural scar adhesion in laminectomy sites treated with saline (Figure 3A), PLA (Figure 3B), MMC (Figure 3C) or MMC-PLA (Figure 3D). The laminectomy sites treated with saline showed obvious epidural scar tissue with many adhesions to the dura mater. The laminectomy sites of rats treated with PLA showed little epidural scar tissue with moderate adherence to the dura mater. The laminectomy sites of rats treated with PLA showed little epidural scar tissue with moderate adherence to the dura mater. The laminectomy sites of rats treated with PLA showed little epidural scar tissue with moderate adherence to the dura mater. The magnifications were 400× (n=8). Masson staining of the laminectomy sites showed that there were abundant collagen fibers in the saline and PLA groups, as demonstrated by the dark blue staining. The number of blue collagen fibers was significantly lower in the MMC and MMC-PLA groups than in the saline and PLA (Figure 4). Further software-based

![Figure 1. The controlled release of MMC from the MMC-PLA film. The cumulative release of MMC on the 5th, 10th, 15th, 20th, 25th and 30th days.](image-url)
Figure 2. Post-operative scar adhesion evaluated by MRI. MRI of the laminectomy sites treated with saline, polylactic acid (PLA), mitomycin C (MMC) or MMC-PLA. (A, Laminectomy area, B, Epidural space, C, Spinal cord area, D, Intervertebral disc or vertebral region). Quantitative analysis revealed that the scar areas of rats treated with MMC-PLA are significantly thinner than those of the rats treated with saline, PLA, or MMC (mm², n = 8, **p < 0.001).

Figure 3. Representative histological images of epidural scar adhesion in laminectomy sites. Histological images of epidural scar adhesion in laminectomy sites treated with saline (A), PLA (B), MMC (C) or MMC-PLA (D).
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Analysis of the IOD of the blue-stained area showed substantial collagen deposition in the laminectomy sites of rats treated with saline and PLA. There was significantly less collagen deposition in the laminectomy sites of rats treated with MMC or MMC-PLA than in those of rats in the saline and PLA groups. Compared with the collagen deposition in the MMC group, the collagen density in the MMC-PLA group was even more significantly reduced (p < 0.01) (Figure 4).

**Analysis of Autophagy-Related Proteins**

Fibroblast autophagy may contribute to fibrosis. Therefore, ATG5, beclin 1, LC3B-2, LC3B-1 and a tumor suppressor protein (p53), which are related to autophagy, were detected by Western blotting. The levels of ATG5, beclin 1, LC3B-2/1, and p53 in the scar tissue from rats treated with MMC or MMC-PLA were significantly greater than those of the animals treated with saline or PLA (p < 0.01). Moreover, the levels of ATG5, beclin 1, LC3B-2/1, and p53 in the MMC-PLA group were significantly greater than those in the MMC group (p < 0.01, Figure 5).

**miRNA Microarray and Real-Time PCR Analyses of Autophagy-Related miRNAs**

Endogenous non-coding 22-nt RNAs (miRNAs) target mRNAs for translational repression and regulate programmed cell death via autophagy. The results of the autophagy-related miRNA microarray showed that the expression levels of 44 different miRNAs were significantly decreased, while 32 miRNAs increased by at least 1.5-fold. The levels of miR-34a, miR-146a, miR-200 were significantly increased, and those of miR-16, miR-221 and miR-378a were significantly decreased in the MMC-PLA group compared with the saline group (Figure 6). We further used real-time PCR to detect the expression of miR-16, miR-34a, miR-146a, miR-200 and miR-221 and miR-378a in scar tissue from the four groups. The expression levels of miR-34a, miR-146a, and miR-200 in the scar tissue of rats treated with saline or PLA were significantly lower than in those treated with MMC-PLA or MMC. Similarly, the expression levels of miR-16, miR-221 and miR-378a in the scar tissue from the four groups. The expression levels of miR-34a, miR-146a, and miR-200 in the scar tissue of rats treated with saline or PLA were significantly lower than in those treated with MMC-PLA or MMC. Similarly, the expression levels of miR-16, miR-221 and miR-378a in the scar tissue from the four groups. The expression levels of miR-34a, miR-146a, and miR-200 in the scar tissue of rats treated with saline or PLA were significantly lower than in those treated with MMC-PLA or MMC (Figure 6, p < 0.01). The expression levels of miR-146a, miR-200 and miR-34a in the scar tissue of rats treated with MMC-PLA were significantly higher than those from rats treated with MMC-PLA or MMC (p < 0.01).
Figure 5. The expression of ATG5, beclin 1, LC3B-2/1 and p53 in scar tissue from rats treated with saline, PLA, MMC or MMC-PLA. **A**, Representative Western blots showing the levels of ATG5 and beclin 1. **B, C**, The results of a quantitative analysis of the ATG5 and beclin 1 protein expression. **D**, Representative Western blots showing the levels of LC3B-2/1 and p53. **E, F**, The results of a quantitative analysis of LC3B-2/1 and p53 protein levels (n = 8, **p < 0.01**).
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Discussion

Epidural scar tissue has been implicated, but has not yet been directly proven, to underlie the pathogenesis of post-surgery pain following a laminectomy\(^2\). Different anti-adhesion strategies have been employed to reduce the formation of scars and spinal stenosis\(^1\),\(^2\),\(^3\) to improve clinical outcomes\(^2\),\(^4\). In recent years, MMC has been widely used to control surgical scar hyperplasia\(^2\),\(^5\) due to its strong cytotoxic effects on fibroblasts; MMC inhibits DNA replication, thereby inhibiting fibroblast mitosis and proliferation\(^3\). Therefore, MMC has been used to prevent epidural scar hyperplasia and to avoid spinal stenosis, which might improve the surgical recovery and quality of life of patients\(^2\),\(^5\). However, when MMC was injected or applied at a high concentration, it not only hindered scar tissue formation but also delayed wound healing, even causing experiment failure due to its cytotoxicity\(^3\). Su et al\(^2\) reported that the optimum concentration of MMC is 0.01% because this concentration exerted the same inhibitory effect on scar hyperplasia as a 0.05% concentration but without causing the side effects of high concentrations. This result is in line with the findings of our previous study\(^2\). However, MMC cannot continuously prevent epidural scar hyperplasia, and it cannot act as a physical barrier. We previously designed a controlled-release drug delivery system (CRDDS) combining a low dose of MMC with polyethylene glycol (PEG) film to produce MMC-PEG film, which could prevent epidural scar adhesions more effectively than using MMC alone\(^3\). In this study, we combined a low dose of MMC with PLA film, which has greater biocompatibility and degradability than PEG film\(^4\),\(^5\). PLA film has been widely used in suture materials, prostheses, implants, and adhesion barrier films to prevent postoperative adhesion\(^4\),\(^5\). First, we successfully established an L1 laminectomy model using SD rats and noted that MMC-PLA had no clear effect on wound healing or neuromotor function. Second, using MRI and histomorphology, we observed that MMC-PLA could reduce scar formation and prevent adhesion between the dura mater and the scar tissue. These findings demonstrated that MMC, which was continuously released from the film and permeated the spinal canal microenvironment, inhibited the proliferation of epidural fibroblasts as the PLA decomposed. Third, we studied five autophagy-related proteins to investigate the relationship between MMC-PLA and fibroblast autophagy because autophagy was observed in MMC-treated apoptotic fibroblasts\(^4\). Atg5 promotes autophagy and inhibits apoptosis\(^4\),\(^5\). Beclin 1 contributes to autophagy by binding to Bcl-2 and inhibits autophagy by binding to Bax\(^4\). Xu et al\(^4\) found that hydroxycamptothecin (HCPT) can induce autophagy in human tendon fibroblasts through beclin 1-related pathways. In the process of autophagy, cytoplasmic LC3B is digested to produce the autophagy marker LC3B-2; therefore, the LC3B-II/LC3B-I ratio can be used to assess the extent of autophagy. The p53 protein can induce autophagy when it binds to damage-regulated autophagy modulator (DRAM)\(^4\). Compared with MMC alone, MMC-PLA significantly increased the expression of fibroblast autophagy-related proteins because it could control the release of MMC, prolonging the duration of drug action. Furthermore, we measured the expression of characteristic miRNAs known to regulate fibroblast autophagy\(^4\). Our results suggested that there were significant changes in miRNA expression in the epidural scar tissue that were induced by MMC-PLA. We further discovered that MMC-PLA decreased hyperplasia and adhesion of the scar by up-regulating miR-34a, miR-146a and miR-200 and down-regulating miR-16, miR-221 and miR-378a, which are closely associated with autophagy\(^4\),\(^5\). These results suggested that MMC-PLA not only inhibited adhesion by providing a physical barrier.

![Figure 6. Expression of miRNAs in the scar tissue of rats. The expression levels of miR-34a, miR-146a, and miR-200 were significantly higher and those of miR-16, miR-221 and miR-378a were significantly lower in the MMC-PLA group than in the saline group.](image-url)
Figure 7. The expression of miR-16, miR-34a, miR-146a, miR-200, miR-221 and miR-378a in the scar tissue of rats treated with saline, PLA, MMC and MMC-PLA. The results of quantitative analyses of the expression of (A) miR-34a (B) miR-146a (C) miR-200 (D) miR-16 (E) miR-221 (F) miR-378a. There were significant differences between the MMC-PLA group and the MMC group in the expression of miR-16, miR-34a, miR-146a, miR-200, miR-221 and miR-378a (n=8, **p < 0.01).
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between the *dura mater* and the scar tissue but also prevented epidural scar hyperplasia by inducing fibroblast autophagy. In an ongoing study, we are performing selective up-regulation or down-regulation of the six aforementioned miRNAs to further investigate how they are involved in the induction of fibroblast death and the prevention of scar formation by MMC-PLA; the aim is to determine the mechanism by which MMC-PLA prevents the adhesion of epidural scars. Our present results suggest that MMC-PLA has a wide range of applications in the prevention of scar formation after laminectomy. MMC-PLA has the following advantages: (1) the physical barrier provided by the membrane structure can directly isolate the dura and the nerve root from the surrounding tissue; (2) the function of the drug target and release in situ has no side effects on other tissues or organs; (3) the inhibitory effect of MMC on the scar can last for a relatively long period by slowly releasing the drug; (4) reducing the dosage and administration frequency of the drug can reduce adverse reactions; (5) the combination of MMC and PLA is a physical mixture instead of a chemical reaction and does not affect the chemical structure or the efficacy of MMC; and (6) MMC-PLA can reduce scar formation, possibly by inducing the autophagy of fibroblasts without causing damage to the peripheral nerve tissue. However, there are potential limitations associated with this study. First, we only evaluated the effect of MMC-PLA on scar formation one-month post-surgery; therefore, the long-term effects are not known. Second, the small sample size was also a potential limitation of our study. Third, animal studies do not always reflect clinical efficacy. For example, we cannot rule out the possibility that even low-dose MMC might be deleterious rather than beneficial in clinical practice, e.g., by potentially inhibiting wound healing post-laminectomy. Fourth, the application of the MMC-PLA film may also have contraindications after laminectomy. For example, it is not recommended that this film is used when the spinal dura mater is injured during surgery. This is because the application of the film might inhibit the healing of the spinal dura mater, resulting in persistent dural leakage or even nerve injury. Fifth, the MMC-PLA film could indeed prevent epidural scar hyperplasia in our study, but it is worth noting that annular fibrosis after discectomy, which could prevent future discectomy or cause cyst recurrence, might also be inhibited. Furthermore, due to the small size of the animals, the local circumstances that would occur in patients with spinal stenosis could not be fully simulated, so the results may not be clinically applicable. Finally, we should emphasize that epidural fibrosis is only one potential reason for post-operation pain. Therefore, anti-scar strategies, whether they employ MMC-PLA or other substances, may not meet the expectations of patients suffering from non-fibrosis-associated pain. More work should be performed in the future to improve the aforementioned limitations.

**Conclusions**

The controlled-release MMC-PLA film could alleviate epidural scar hyperplasia after laminectomy; this outcome might be associated with increased autophagy and altered expression of miRNAs in the scar tissue. MMC-PLA film may be used as an effective physical and chemical barrier to alleviate epidural scar adhesion post-laminectomy.

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**Conflict of Interest**

The Authors declare that they have no conflict of interests.

**References**


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