The effectiveness of poloxamer 407-based new anti-adhesive material in a laminectomy model in rats

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Abstract

Purpose In the laminectomy model in rats, to verify anti-adhesive effectiveness of the new material, a mixture composed of poloxamer 407, calcium chloride, and xanthorhizol, we compared it with that of commercially used solution form anti-adhesive agent GUARDIX-SL, Biorane. **Materials and methods** A total of 108 Sprague–Dawley rats (SD rats) were divided equally into three groups: negative control group (NCG), positive control group (PCG), and experimental group (EG). After exposing the dura on L4 level, we closed the wound shortly after hemostasis, after administering the anti-adhesive agent. To evaluate effectiveness, 18 SD rats from each group were killed after 1 week of rearing. Nine were examined by grading of gross adhesion and the other nine, by grading of histological adhesion. The degree of adhesion in the remainder of 18 SD rats in each group was examined with the same method after four weeks of rearing.

Results Comparing the degree of adhesion after growth for 1 week, the gross and histological adhesion of the EG was lower than that of the NCG. There was no statistical significance in the gross score ($P = 0.63$), but there was statistical significance in the histological score ($P = 0.04$). The EG showed similar or improved degrees of adhesion in comparison with the PCG. In comparison after growth for 4 weeks, although gross adhesion of the EG was not significantly lower than the NCG, histological adhesion was remarkably low in the EG ($P = 0.01$). The EG showed similar or improved degrees of gross and histological adhesion in comparison to that of the PCG. ($P = 0.20$, 0.07).

Conclusion The new anti-adhesive material showed similar or improved effectiveness with the existing agents for commercial use. This result suggests that the new anti-adhesive material will be a successful candidate as a future product for clinical use.

Keywords Epidural adhesion · Anti-adhesion · Laminectomy

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Introduction

Adhesion is an inevitable result that occurs during the healing process of injured tissues. Perineural fibrosis and adhesion that occur after decompression surgery of the spine is considered one of the major causes of poor clinical outcomes, such as postoperative chronic low back pain and radiating pain through traction of the dura or nerve roots [1–3]. Approximately, 15% of post-laminectomy patients have postoperative symptoms related to the fibrosis and adhesion [4]. Post-laminectomy epidural fibrosis significantly increases the hazards of revision spine surgery and

may contribute to the occurrence of failed back syndrome [5, 6]. Therefore, many researchers are conducting studies on operative methods and new materials that would help in reducing adhesion. Epidural fibrosis is known because of proliferation of fibroblast originating from paraspinal muscles and periosteum ingrowing into the postoperative hematoma [2, 4, 7].

Anti-adhesive agents, used after decompression surgery of the spine recently, serve as a barrier that separates the dura and hematoma mechanically, demonstrating anti-adhesion effects. To achieve sufficient anti-adhesion effects, this barrier must stay for a certain period of time in between the dura and its surrounding tissues. However, when there is no more adhesion and fibrosis development after the healing process has completed, the barrier must be resolved or absorbed into the body, not remaining as a foreign body. Last, it must be nontoxic [8].

Materials that are qualified for the prerequisites above are mostly synthetic or bio polymers. They are developed in various types ranging from solution, gel to membrane. Among them, the solution type anti-adhesive agent may have limitations in the barrier's role, because it cannot fixate on a certain region due to its characteristic of liquidity. The membrane type may be difficult to be deformed in accordance with the shape of exposure of the dura, or its separation from surrounding tissues may be incomplete. A new anti-adhesive material, a mixture composed of poloxamer 407 [9], calcium chloride, and xanthorrhizol, has been developed to appear as a solution form at low temperatures, but transform into a gel form at normal or body temperature. When the new material is refrigerated with ice and sprayed onto a desirable region, it turns into a semisolid form, fixating on the sprayed area. It can be considered a supplementary material that remedies shortcoming of the current solution and membrane types. The purpose of this study is to confirm anti-adhesion effects of the new material by comparing it with that of GUARDIX-SL (Biorane, Seoul, Korea), a solution type anti-adhesive agent for commercial use, in the laminectomy model in rats.

Materials and methods

Experimental animals

This study employed about 10-week-old Sprague–Dawley rats (SD rats), weighing from 320 to 350 g. A total of 121 SD rats were mobilized for the experiment. Tests were conducted on the rats until the number of randomly selected rats reached 36 in each of the three groups: the positive control group, the negative control group and the experimental group. L4 laminectomy was performed on

the experimental animals, conforming to the study plan approved by the Seoul National University Institutional Animal Care and Use Committee (SNUIACUC). 10 rats whose dura were injured during surgery and 3 rats that were severely infected during the experiment were excluded from the study samples.

Materials

The material used in this study is a physical mixture that is mainly composed of poloxamer 407 (23 wt.%, BASF, Ludwigshafen, Germany), and of calcium chloride (0.5 wt.%) and xanthorrhizol (0.05 wt.%) as additives in an aqueous solution form. Calcium chloride was added to help hemostasis by calcium ion, while xanthorrhizol [10], which is extracted from *Curcuma xanthorrhiza*, was additionally applied to generate anti-bacterial and anti-inflammatory effects. Calcium chloride and xanthorrhizol is a trace and the mechanical property of new material is identical to that

Fig. 1 Phase transition. New material is solution form when under 20°C (a). Getting warmth (22°C), phase transition is occurred into gel form (b)

of poloxamer 407, and sol-gel transition temperature is determined by density of poloxamer 407. This material appears as a solution type at temperatures below 22°C and as a gel type above that temperature (Fig. 1). Such phase transition feature, a phenomenon resulting from hydrophobic interaction of poloxamer 407 aqueous solutions, occurs as the result of interaction among polypropylene groups above a certain temperature [9]. Poloxamer 407 remains within the body as a gel form for 6–7 weeks before being absorbed and excreted in animal study [11].

Methods

All operations were performed by the first author of the study. Zoletil (20 mg/kg) and Xylazine were used for general anesthesia. After depilation and disinfection of the lumbar region, the conventional midline approach was employed to get the L4 lumbar area exposed. The L4 laminar was removed with a burr, and the dura was carefully exposed without damage. The dura exposure averaged 5.8 mm². After exposing the dura, efforts were made to achieve nearly complete hemostasis. The wounds of the rats in the negative control group were closed layer by layer with interrupted suture shortly after the dura exposure. As for the positive control group, 0.05 mL of GUARDIX-SL was applied onto the dura with 1 mL syringe. GUARDIX-SL, a mixture of equal amounts of hyaluronic acid and sodium carboxymethyl cellulose, is widely used for reducing adhesion [12, 13]. In the experimental group, after being refrigerated with ice, 0.05 mL of the new anti-adhesive material was administered using 1 mL syringe. Then, the wounds of the rats were closed in the same manner (Fig. 2). After the operations, an intramuscular injection of antibiotics (Cefazolin 0.5 mL) was administered and the rats were raised without any intervention.

Evaluation of gross adhesion

One or 4 weeks following the operations, the experimental animals were killed using a CO₂ chamber under the guidelines for euthanasia, and the operation sites were probed again. From each group, nine rats that were raised for 1 week and nine rates raised for 4 weeks were selected to be used for an evaluation of gross adhesion. To prevent bias, the investigator of this study was blinded to the surgical information. After the paraspinal muscle was gently removed, the laminectomy site was probed with a microforcep. The amount of adhesion was judged based on the Rydell standard (Table 1) [14–16]. When surrounding bones overgrew into the surgical site, making it impossible to re-expose the dura, it was judged as complete adhesion.

Fig. 2 Exposure of dura mater (a) and apply of anti-adhesive agent. GUARDIX-SL (Biorane, Seoul, b) and new material (c)

Evaluation of histological adhesion

After killing the experimental animals based on the same method, the vertebral bodies from L3 to L6 were removed en bloc including the paraspinal tissue and fixed in

Table 1 Rydell standard [14–16]

Grade 0	Peridural scar tissue was not adherent to the dura meter
Grade 1	Peridural scar tissue was adherent to the dura but easily dissected
Grade 2	Peridural scar tissue was adherent to the dura, and there was difficulty in dissecting it without disrupting the dura
Grade 3	Peridural scar tissue was firmly adherent to the dura and could not be dissected

Table 2 Definition of criteria employed for scoring for histologic analysis (Barbera et al. [17])

Grade 0 (none)	Absence of fibrosis
Grade 1 (minimal)	Fibrosis not adherent to the dural sac or nerve roots, less than 25% involvement
Grade 2 (moderate)	Fibrosis adherent to the dural sac or nerve roots, less than 50% involvement
Grade 3 (extensive)	Fibrosis adherent to the dural sac and nerve roots, less than 75% involvement
Grade 4 (severe)	Fibrosis throughout the vertebral canal encompassing the dural sac and nerve root, up to 100% involvement

formalin. The specimens were cut into 5 mm thick sections with a power saw to embrace the surgical site, and then were soaked in the decalcifying agent (Shandon TBD-1 Decalcifier, Thermo scientific, Michigan, USA) for 72 h for decalcification. After soaking, they were washed out with PBS solution and underwent paraffin embedding. Histological slides were made by cutting the center of the surgical site, and then stained with hematoxylin and eosin. To examine the degree of histological adhesion, this study adopted the method by Barbera et al. [17] (Table 2) and the investigator did not have any information about surgery to reduce bias.

Statistical analysis

For evaluation of anti-adhesion effects of the new material, the degree of adhesion was compared between the experimental group and the positive control group, and between

the experimental group and the negative control group. Comparison of the degree of gross adhesion and histological adhesion was performed using the Mann-Whitney test (SPSS V17.0, Chicago) in the classified groups of the rats grown for a week and the rats grown for 4 weeks. A probability below 0.05 was determined as statistically significant.

Result

1 week evaluation

In the evaluation of gross adhesion, six samples showed grade 0 adhesion both in the experimental and positive control group, achieving similar results. In the negative control group, five samples showed grade 0 adhesion. Adhesions that are more severe than grade 2 were not observed in all of three groups (Table 3).

When examined under the microscope, more fibrous tissues were observed in the negative control group, compared with the two other groups. In the positive control group and the experimental group, it was confirmed that the anti-adhesive agent had clearly separated the dura and fibrous tissue (Fig. 3).

In the evaluation of histological adhesion, grade 4 adhesion was found in the largest share of five samples in the negative control group. Grade 1 adhesion was found in four samples in the positive control group. In the experimental group, grade 1 and grade 2 adhesions were found in three samples each, showing lower degrees of adhesion than the negative control group (Table 3).

When each grade was calculated into scores, the scores of gross adhesion and histological adhesion of the negative control group stood at 0.4 ± 0.5 and 3.2 ± 1.1 , respectively. Those of the positive control group posted 0.3 ± 0.5 and 2.7 ± 1.4 . The experimental group showed 0.3 ± 0.5 and 2.1 ± 1.1 . In comparison of the experimental group with the negative control group, it turned out that the experimental group's scores for both gross and histological adhesion were lower than those of the negative control group. There was no statistical significance in the gross score ($P = 0.63$), but there was statistical significance in

Table 3 Result of adhesion at 1 week post-surgery

	Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gross Adhesion	NCG	5	4	0	0	
	PCG	6	3	0	0	
	EG	6	3	0	0	
Histological Adhesion	NCG	0	1	1	2	5
	PCG	0	4	1	1	3
	EG	0	3	3	2	1

NCG negative control group,
PCG positive control group,
EG experimental group

Fig. 3 The laminectomy sites of each groups under $\times 4$ magnification. Negative control group (a), positive control group (b) and experimental group (c). Dense fibrous tissue (FT) was observed adhering to the dura (black arrow, a). Anti-adhesive material (*) acting as a barrier between the fibrous tissue and the dura (b, c). (1 week post-surgery, H–E stain. NT neural tissue)

the histological score ($P = 0.04$). In comparison between the experimental group and the positive control group, there was no significant difference both in the scores of gross adhesion and histological adhesion ($P = 1.00, 0.33$, Fig. 4).

Fig. 4 Comparison of adhesion score at 1 week post-surgery. There was significant difference between NCG and EG at histological adhesion score ($*P < 0.05$, NCG negative control group, PCG positive control group, EG experimental group)

4 weeks evaluation

After 4 weeks of growth, the degree of gross adhesion was found as follow. In the negative control group, most of the samples showed severe degrees of adhesion equivalent to grade 3. On the other hand, most samples in the positive control group and the experimental group showed low degrees of adhesion, less than grade 2.

Under the microscope, remodeling of fibrosis with neo-vascularization was observed in the negative control group. In the experimental group, severe fibrosis was observed similarly in the negative control group, but some remnants of the new material showed separating neural tissue and fibrous tissue (Fig. 5).

As for the degree of histological adhesion, all of the samples in the negative control group were found grade 4. In the positive control group, four cases showed lower degrees of adhesion than the negative control group. However, in the experimental group, seven cases were found with lower degrees of adhesion than the negative control group (Table 4).

When the same calculation method was applied to the grades, the negative control group awarded a score of 2.8 ± 0.4 and 4 for gross adhesion and histological adhesion, respectively, while the positive control group received a score of 1.8 ± 1.0 and 3.3 ± 0.9 . The experimental group received 2.3 ± 0.7 for gross adhesion and 2.9 ± 0.8 for histological adhesion. In comparison of the experimental group with the negative control group, like shown in the case of the 1-week reared rats, the

Fig. 5 The laminectomy site of the negative control group (a) and the experimental group (b) under $\times 4$ magnification. a Severe fibrous tissue (FT) with neo-vascularization (black arrow) is shown near the dura (black arrow head). b Some remnants of the new material (white arrow) separate the dura and the fibrous tissue (FT) (4 weeks post-surgery, H-E stain, NT neural tissue)

experimental group showed small degrees of adhesion both grossly and histologically. Especially, in the histological comparison, the adhesion in the experimental group was significantly lower than that of the negative control group

Table 4 Result of adhesion at 4 weeks post-surgery

	Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Gross adhesion	NCG	0	0	2	7	
	PCG	1	2	4	2	
	EG	0	1	4	4	
Histological adhesion	NCG	0	0	0	0	9
	PCG	0	0	2	2	5
	EG	0	0	3	4	2

NCG negative control group,
PCG positive control group,
EG experimental group

Fig. 6 Comparison of adhesion score at 4 weeks post-surgery. There was significant difference between NCG and EG at histological adhesion score. (* $P < 0.05$, NCG negative control group, PCG positive control group, EG experimental group)

($P = 0.01$). In comparison between the experimental group and positive control group, the experimental group awarded a lower score of histological adhesion than the positive control group, but there was no statistical significance found ($P = 0.07$, Fig. 6).

Discussion

Postoperative fibrosis and adhesion is a physiological phenomenon that normally occurs during the healing process of injured tissue. It is an inflammatory reaction caused by organization of the fibrin matrix within the damaged tissue, resulting from exudation of fibrinogen and proliferation of fibroblasts [18]. However, excessive fibrosis or adhesion to surrounding tissues could have unintended consequences. In particular, after laminectomy of the spine, fibrosis or adhesion occurring in the dura and nerve roots would trigger tethering of nerves, causing continuous neurologic symptoms or increasing risks of nerve injuries

while in motions. Furthermore, when a revision is needed, fibrosis increases risks of the dura or nerve root injury, leading to poor clinical outcomes that are called “failed back syndrome” [5, 6].

As concerns about adhesion and its clinical significance increased, Holtz [19] proposed a five-phase method to reduce adhesion: (1) reducing the initial inflammatory reaction and subsequent exudate release; (2) inhibiting coagulation of this exudate; (3) promoting the removal of fibrin deposition; (4) mechanically separating fibrin-covered surfaces; and (5) inhibiting fibroblastic proliferation. As attempts to reduce the initial inflammatory reaction and the exudates release, various methods were used: alteration of surgical methods such as microdiscectomy [20], use of anti-inflammatory medications [21, 22]. Bio and synthetic substances such as fat [3, 23, 24], Gel form and Avitene [21], Silastic [3], Polylactic acid [7], Gore-Tex membranes [25] were used based on a theoretical background that they can separate the nerve tissue (the dura and nerve roots) from its surrounding tissues (the paraspinal muscles and periosteum). However, they demonstrated relatively limited results [23, 26].

Recently, there are numerous studies being conducted on new materials serving as the barrier that separates the nerve tissue from surrounding tissues [27, 28]. To have sufficient anti-adhesion effects, a barrier must have the following characteristics: (1) the barrier must remain between two different tissues for a certain period of time, so the tissues do not come into contact with each other. (2) the barrier must be absorbed into the body and not remain as a foreign body after the healing process [8]. Materials that are recently used in such studies are mostly bio or synthetic polymer materials, successfully stratifying these conditions.

GUARDIX-SL used as a positive control is a viscous solution form consisting of a mixture of hyaluronic acid (HA) and sodium carboxymethyl cellulose (CMC) in 1:1 ratio. This substance is authorized to be used as an anti-adhesive substance in South Korea, and favorable results are being reported [12, 13, 29]. Hyaluronic acid, which exists in the body especially in the connective tissues, has anti-adhesion effect and enhances healing process [30, 31]. Carboxymethyl cellulose, is a high-molecular weight polysaccharide, and acts as a mechanical barrier for reducing adhesion after surgery [32].

The material used in this study is a physical mixture that is mainly composed of poloxamer 407 (BASF, Ludwigshafen, Germany), and calcium chloride and xanthorrhizol as additives in an aqueous solution form. Poloxamer, a substance composed of nonionic triblock copolymers of the central hydrophobic polypropylene and side hydrophilic polyethylene, is extensively used as a surfactant owing to its amphiphilic feature. Oh et al. [33] reported that

poloxamer is a good anti-adhesive agent playing the barrier's role appropriately, because it showed fairly good anti-adhesion effects, had small inflammatory reaction and non-toxicity within the body in a study using the peritoneum adhesion model in rats. Reigel et al. [34] also said that the substance had about 50% of anti-adhesion effects in an experimental study using the laminectomy model in rabbits, affirming that poloxamer is a useful anti-adhesive agent in spine surgery. This study also found that the new material successfully prevented grade 1 or higher degrees of adhesion in all comparisons between the experimental and negative control group.

Existing commercialized anti-adhesive agents that play the roles of the barrier are in the form of solution, gel or membrane. The membrane type is easy to handle and can be cut into a shape that fits the form of the exposed area. However, when the membrane type is taken to be used, it is crucial to ensure coverage of nerves in the marginal area after laminectomy, or otherwise anti-adhesion effects could be reduced due to proliferating fibrous tissues in gaps between the barrier and tissues [23, 25]. For the solution type, regardless of the shape of the exposed area after laminectomy and of concerns over incomplete coverage of the nerves in the marginal area, the agent can be easily applied to surgery. However, the solution type agent cannot be fixed onto the surgical site due to its physical traits including mobility. A gel type agent can secure almost complete coverage of the nerves in the marginal area regardless of the shape of the exposed area and has high shape molding capacity or space filling effects, which is good for nerve protection. However, a problem is that the material is relatively difficult to handle [28]. The new anti-adhesive material was developed to remedy shortcomings of each type of the existing anti-adhesive agents. Its physical characteristics vary in line with changes in the temperature. At low temperatures, the new material appears as a solution type, being easy to handle, guaranteeing complete coverage and fixating on the surgical site, as it can be transformed into a semi-solution type like gel at the body temperature. Touting these features as strengths, the new material is expected to have greater anti-adhesion effects than the solution type, and it turned out that the new material demonstrated fairly good preventive effects despite little statistical significance found in comparison of the experimental group with the positive control group.

Although there are several types of thermoresponsive anti-adhesive materials developed and studied, studies on the use after spine surgery are rare, and no material has received FDA approval [35]. Material that was used in this study is biocompatible as stated above. It showed a comparably effective anti-adhesive result under simple method for use. This leads us to consider it to become one of the commercially viable anti-adhesive materials in the future.

Unlike numerous studies conducted on rabbits to prove anti-adhesion effects in them after laminectomy [7, 27, 28], this study used the laminectomy model in rats to examine effectiveness of the new anti-adhesive material. However, there were difficulties in judging degrees of gross adhesion, in particular, because the exposed area of the dura and nerve roots was as small as 4–9 mm², which is very characteristic of the experimental animals. Moreover, it is concerned that bias could be found in the study method in terms of judging the degree of gross adhesion, because judgment for each group was made at different times. Another problem in this study method is that there is no way to ascertain inter-observer agreement or intra-observer agreement, because researchers are not allowed to double-check the result after the re-probe. In addition, most of the studies concerning anti-adhesion effect of poloxamer 407 were in vivo based on the animal studies. Therefore, there is a possibility that a desirable amount of anti-adhesion effects could not be achieved when it is actually used in a clinical test. Therefore, further studies are deemed necessary.

Conclusion

The new anti-adhesive material is easily applicable to the surgical site, ensures complete coverage of the nerves and is able to fixate on a wanted area for a certain period of time, owing to its phase transition feature which enables it to transform from solution to gel (sol-gel) at different temperatures. In comparison with the currently commercialized solution type anti-adhesive agent, this new material had similar or improved effects of anti-adhesion. Although further experiments for clinical use will be needed, the new material can be considered as a successful candidate for a new anti-adhesive agent that will do help reduce fibrosis and adhesion in the dura and surrounding tissues caused by laminectomy.

Conflict of interest None.

References

- Benoist M, Ficat C, Baraf P, Cauchoix J (1980) Postoperative lumbar epiduro-arachnoiditis. Diagnostic and therapeutic aspects. *Spine (Phila Pa 1976)* 5:432–436
- LaRocca H, Macnab I (1974) The laminectomy membrane. Studies in its evolution, characteristics, effects and prophylaxis in dogs. *J Bone Joint Surg Br* 56B:545–550
- Quist JJ, Dhert WJ, Meij BP, Visser WJ, Oner FC, Hazewinkel HA, Verbout AJ (1998) The prevention of peridural adhesions. A comparative long-term histomorphometric study using a biodegradable barrier and a fat graft. *J Bone Joint Surg Br* 80:520–526
- Lee HM, Yang KH, Han DY, Kim NH (1990) An experimental study on prevention of postlaminectomy scar formation. *Yonsei Med J* 31:359–366
- Ross JS, Robertson JT, Frederickson RC, Petrie JL, Obuchowski N, Modic MT, deTribotet N (1996) Association between peridural scar and recurrent radicular pain after lumbar discectomy: magnetic resonance evaluation. *ADCON-L European Study Group. Neurosurgery* 38:855–861 discussion 861–853
- Robertson JT (1996) Role of peridural fibrosis in the failed back: a review. *Eur Spine J* 5(Suppl 1):S2–S6
- Mikawa Y, Hamagami H, Shikata J, Higashi S, Yamamuro T, Hyon SH, Ikada Y (1986) An experimental study on prevention of postlaminectomy scar formation by the use of new materials. *Spine (Phila Pa 1976)* 11:843–846
- Kwon SW, Lim SH, Lee YW, Lee YG, Chu BY, Lee JH, Lee YM (2006) Anti-adhesive effect of Poloxamer/Alginate/CaCl₂ mixture in the rat model. *J Korean Surg Soc* 71:280–287
- Dumortier G, Grossiord JL, Agnely F, Chaumeil JC (2006) A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharm Res* 23:2709–2728
- Hwang JK, Shim JS, Baek NI, Pyun YR (2000) Xanthorrhizol: a potential antibacterial agent from *Curcuma xanthorrhiza* against *Streptococcus mutans*. *Planta Med* 66:196–197
- Feng H, Sun J, Jiang P (2008) In vitro and in vivo biodegradation of sustained-release vehicle poloxamer 407 in situ gel. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 22:28–31
- Lee SY, Jeon CW, Lee MB, Lee KR, Koh ES, Uhm YI (2000) A experimental study for the effect of sodium carboxymethyl cellulose on prevention of pericardial adhesion. *Korean J Thorac Cardiovasc Surg* 33:541–546
- Kim JH, Kim KS, Yoon HC, Lee JH, Yoon JH, Song KJ, Park TJ (2005) Anti-adhesive effect of GUARDIX-SL (R) after endoscopic sinus surgery. *Korean J Otolaryngol Head Neck Surg* 48:1478–1483
- Rydell N (1970) Decreased granulation tissue reaction after installment of hyaluronic acid. *Acta Orthop Scand* 41:307–311
- Butler J, Rydell N, Balazs E (1970) Hyaluronic acid in synovial fluid. VI. Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of arthritis in track horses. *Acta Vet Scand* 11:139–155
- Sun Y, Wang LX, Wang L, Sun SX, Cao XJ, Wang P, Feng L (2007) A comparison of the effectiveness of mitomycin C and 5-fluorouracil in the prevention of peridural adhesion after laminectomy. *J Neurosurg Spine* 7:423–428. doi:10.3171/SPI-07/10/423
- Barbera J, Gonzalez J, Esquerdo J, Broseta J, Barcia-Salorio J (1978) Prophylaxis of the laminectomy membrane. An experimental study in dogs. *J Neurosurg* 49:419
- Moll HD, Schumacher J, Wright JC, Spano JS (1991) Evaluation of sodium carboxymethylcellulose for prevention of experimentally induced abdominal adhesions in ponies. *Am J Vet Res* 52:88–91
- Holtz G (1980) Prevention of postoperative adhesions. *J Reprod Med* 24:141–146
- Tullberg T, Rydberg J, Isacson J (1993) Radiographic changes after lumbar discectomy. Sequential enhanced computed tomography in relation to clinical observations. *Spine (Phila Pa 1976)* 18:843–850
- Jacobs RR, McClain O, Neff J (1980) Control of postlaminectomy scar formation: an experimental and clinical study. *Spine (Phila Pa 1976)* 5:223–229
- Olmarker K (2010) Reduction of adhesion formation and promotion of wound healing after laminectomy by pharmacological inhibition of pro-inflammatory cytokines: an experimental study in the rat. *Eur Spine J* 19:1–5

23. Gill GG, Sakovich L, Thompson E (1979) Pedicle fat grafts for the prevention of scar formation after laminectomy. An experimental study in dogs. *Spine (Phila Pa 1976)* 4:176–186
24. Langenskiöld A, Kiviluoto O (1976) Prevention of epidural scar formation after operations on the lumbar spine by means of free fat transplants. A preliminary report. *Clin Orthop Relat Res* 115:92–95
25. Neel HB 3rd (1983) Implants of Gore-Tex. *Arch Otolaryngol* 109:427–433
26. Songer MN, Ghosh L, Spencer DL (1990) Effects of sodium hyaluronate on peridural fibrosis after lumbar laminotomy and discectomy. *Spine (Phila Pa 1976)* 15:550–554
27. Temel SG, Ozturk C, Temiz A, Ersozlu S, Aydinli U (2006) A new material for prevention of epidural fibrosis after laminectomy: oxidized regenerated cellulose (interceed), an absorbable barrier. *J Spinal Disord Tech* 19:270–275
28. Alkalay R, Kim D, Urry D, Xu J, Parker T, Glazer P (2003) Prevention of postlaminectomy epidural fibrosis using bioelastic materials. *Spine* 28:1659–1665
29. Oh TH, Paik JS, Yang SW (2010) Results of the mixed solution of hyaluronate and sodium carboxymethylcellulose in endonasal dacryocystorhinostomy. *J Korean Ophthalmol Soc* 51:159–163
30. Becker JM, Dayton MT, Fazio VW, Beck DE, Stryker SJ, Wexner SD, Wolff BG, Roberts PL, Smith LE, Sweeney SA (1996) Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *J Am Coll Surg* 183:297
31. Reijnen MMPJ, Meis JFGM, Postma VA, van Goor H (1999) Prevention of intra-abdominal abscesses and adhesions using a hyaluronic acid solution in a rat peritonitis model. *Arch Surg* 134:997
32. Elkins T, Bury R, Ritter J, Ling F, Ahokas R, Homsey C, Malinak L (1984) Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat I. *Fertil Steril* 41:926
33. Oh SH, Kim JK, Song KS, Noh SM, Ghil SH, Yuk SH, Lee JH (2005) Prevention of postsurgical tissue adhesion by anti-inflammatory drug-loaded pluronic mixtures with sol-gel transition behavior. *J Biomed Mater Res A* 72:306–316. doi:[10.1002/jbm.a.30239](https://doi.org/10.1002/jbm.a.30239)
34. Reigel DH, Bazmi B, Shih SR, Marquardt MD (1993) A pilot investigation of poloxamer 407 for the prevention of leptomeningeal adhesions in the rabbit. *Pediatr Neurosurg* 19:250–255
35. diZerega GS, Cortese S, Rodgers KE, Block KM, Falcone SJ, Juarez TG, Berg R (2007) A modern biomaterial for adhesion prevention. *J Biomed Mater Res B Appl Biomater* 81:239–250. doi:[10.1002/jbm.b.30659](https://doi.org/10.1002/jbm.b.30659)