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Comparison of the effects of polyethylene glycol and hyaluronic acid in prevention of epidural fibrosis

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Abstract

The aim of this study was to evaluate of the effect of 5% Polyethylene Glycol 4000 in the prevention of epidural fibrosis and to compare the results with hyaluronic acid. A total of 36 adult New Zealand White Rabbits were used in the study. Three groups were formed with each group including 12 rabbits (Group I: Control, Group II: 5% Polyethylene Glycol 4000, Group III: Hyaluronic acid). Hemilaminectomy was performed at L5 vertebrae on the right side. Three rabbits randomly selected from each group at postoperative 2nd, 4th, 8th and 12th week were euthanized. Macroscopic and histopathological evaluation were performed in terms of the amount of scar tissues. Statistical evaluation was made with Mann-Whitney U Test and Kruskal-Wallis Variance Analysis. $P < 0.05$ was considered statistically significant. In the hemilaminectomy sites of Group I, severe thickness and tenacious epidural scar adhesions were found between the dura mater and surrounding tissues. In the Group II, dura mater was clean without any evidence of adhesion or scar tissue and minimal adhesions were present. In the Group III, moderate adhesion and scar tissue or minimal adhesion and very thin scar tissue were observed. Statistically; Group II was significantly different from Group I ($P < 0.000$) and Group III ($P < 0.002$), and Group III was significantly different from Group I ($P < 0.001$). It was concluded that 5% Polyethylene glycol 4000 can safely be used locally during operation in the area of decompression in order to prevent epidural fibrosis encountered as a postoperative complication after hemilaminectomy.

Key Words: Epidural fibrosis, hemilaminectomy, hyaluronic acid, polyethylene glycol, prevention.

INTRODUCTION

Epidural fibrosis is a serious cause in the natural healing process that occurs after almost every lumbar spinal intervention and constitutes 10% to 24% of cases in failed back surgery syndrome[15,33,47]. The formation of epidural fibrosis (extradural fibrous tissue) is a very gradual process. It occurs the result of invasion of postoperative hematoma and dense fibrous tissue that forms at the periosteum fibrous layer and on the deep surface of the paravertebral muscles. This process that referred to as epidural fibrosis can be developed after laminectomy / hemilaminectomy[15].

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Extreme scar tissue adhering to nerve roots and dura mater is cause continuous pain[8,11,14,15,29,34,47,57]. Although there is no consensus on the proportion of the problems associated with spinal epidural fibrosis, if there is no bone and disk pathology, many studies have focused on the possibility that recurrent symptoms after lumbar spinal operations may be epidural fibrosis[48,50]. Many authors have noted that epidural fibrosis is not only encountered a major difficulty when operation is required, but is also responsible for intraoperative complications and bad postoperative results[3,43].

It has been aimed to prevent epidural fibrosis by using different biological and non-biological materials[7]. For this purpose; ADCON-L (Anti-adhesion barrier gel)[32], omega-3[17], chitin[35], fat grafts[22], resveratrol[55], poly (L-glutamic acid)/ chitosan[37], amniotic membrane[14], omentum greft[10], hyaluronic acid (HA)[26,42], gel and sepra film forms of hyaluronic acid[31,59], rosuvastatin[23], sodium hyaluronate[32], cepea extract-heparin and allantoin mixture[58], aprotinin[36], pimecrolimus[6], aceclofenac[52], mitomycin-C[54], absorbable cement[66], 4% icodextrin[28], and novel biodegradable lamina[40] has been used. However, an acceptable success has not yet been achieved in the prevention or reduction of epidural fibrosis[2,34,57].

Among all methods, autogenous fat grafting studies were found to be more reliable than other approaches[9,19,22,46], and it seems to be the most preferred material in spinal surgery until this day. However, autogenous fat grafting still has a number of concerns, such as seroma, infection, necrosis, cystic deposition, and direct caudal pressure[22]. At the same time, It has been reported that free fat grafts may be resorb[9,19].

Polyethylene Glycol (PEG) 4000 (5%) has been reported to be effective in preventing postoperative intraabdominal adhesions and prevention of adhesions that develop after tenoraphy[12,27]. It has also been reported that combination of Silk-PEG Hydrogels reduced the formation of epidural fibrosis[62]. In another study, combinaton of mitomycin C-PEG film was used in the prevention of epidural fibrosis in postlaminectomy model with positive results[39].

In this experimental study, It was aimed to compare 5% Polyethylene Glycol 4000 and Hyaluronic acid in prevention of epidural fibrosis.

Material and Methods

The experimental study was approved by the Fırat University Ethical Committee of Animal Experiments (Verdict number: 2014/01/05). The project was supported by Fırat University Scientific Research Projects Unit (VF.14.14).

The study material included 36 adult New Zealand White Rabbits weighing 2,2–3,6 kilograms which were obtained from Fırat University Experimental Research Center. Gender discrimination was not observed in the subjects. Three groups were formed with each group including 12 rabbits (**Group I:** 0.9% NaCl, Control, **Group II:** 5% PEG 4000, **Group III:** HA). Each rabbit was numbered from the ears. Rabbits were anesthetized with Ketamine Hydrochloride (35 mg / kg, I.M. Ketalar, Parke-Davis) 5–10 minutes after injection of Xylazine Hydrochloride (5 mg / kg I.M. Rompun, Bayer). It was placed in the prone position on the operating table, after rabbit's back region was shaved from thoracic vertebrae to sacrum. The L5 level was determined by palpation of the iliac wings. Lumbosacral area was cleaned with 10% povidone-iodine solution, then surgical area was covered with a sterile cloths. In the lumbar area, the skin and subcutaneous connective tissue was passed through the middle line with an incision of about 10 cm, the fascia bilaterally was opened and the paravertebral muscles on the right side were subperiostealized in the L4–L6 region. Hemilaminectomy was performed at L5 vertebrae on the right side. Hemilaminectomy defect, 2 mm in wide and 3 mm in long was made with a steel round bur (Figure 1). It was applied 0.9% NaCl 1 ml in Group I, 5% PEG 4000 (Merck, Germany) 1 ml (5% solution of PEG 4000 was prepared by

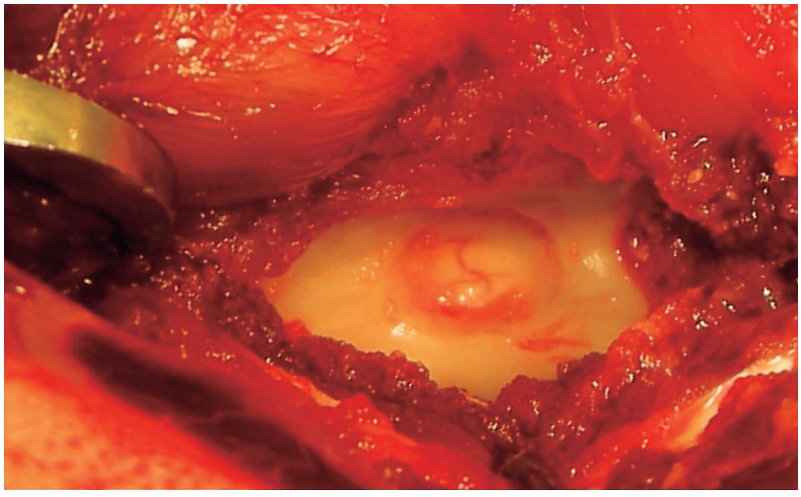

Fig. 1. The appearance of hemilaminectomy in elliptical form with a length of 3 mm on the right side on the L5 vertebra.

boiling 5 g of PEG 4000 in 95 ml of distilled water[27]) in Group II and HA (Ostenil, Switzerland) 1 ml in Group III to the hemilaminectomy region. Subsequently, paravertebral muscles, fascia and subcutaneous connective tissue were closed with 4-0 vicryl and skin sutured with 3-0 silk. Penicillin (30.000 U / kg, Devapen 400.000 U Deva Ilac) and Flunixin Meglumin (1.1 mg / kg, Fundamin, Bavet) were administered intramuscularly to all rabbits postoperatively for 5 days. Until the day of the euthanasia, the subjects were fed on the normal diet without any restrictions in the Center for Experimental Research at Fırat University. Three rabbits randomly selected from each groups at postoperative 2nd, 4th, 8th and 12th weeks were euthanized. The sacrification process was performed with by carbondioxide inhalation method. L4–L6 lumbar vertebrae and muscles were removed in blocks and macroscopic evaluations of the hemilaminectomy area at L5 were performed. Macroscopic evaluation was performed using Epidural Fibrosis Gross Score (Grade 0: No scar or adhesion, Grade 1: Minimal adhesion, very thin scar tissue Grade 2: Moderate adhesion and scar tissue, Grade 3: Dense and very tight adhesion and scar tissue)[48]. The L5 vertebrae that underwent hemilaminectomy were fixed in 10% formalin solution and then subjected to 10 days decalcification in 10% formic acid solution. Paraffin blocks were prepared from the tissue samples that were routinely processed, sections of 5 microns in thickness were prepared with the aid of microtome from the blocks and the obtained preparations were stained with Hematoxylene-Eosin (H.E.) and Masson trichrome method and examined under light microscope (Olympus BX43, DP72) and microscopic pictures were taken. The preparations were graded histopathologically in terms of amount of epidural scar tissue and adhesions (Grade 0: Dura matter is free of scar tissue, Grade I: Presence of only thin fibrous bands between scar tissue and dura matter, Grade II: Continuous adhesions filling less than 2/3 of hemilaminectomy space, Grade III: Adhesions filling more than 2/3 the hemilaminectomy space or/and extend to the nerve roots)[24].

Statistical analysis: Statistical evaluation of the results was made using the SPSS 22.0 statistical package. Two groups were compared with Mann-Whitney U Test, three groups were compared by Kruskal-Wallis Variance Analysis. $P < 0.05$ were considered statistically significant[15].

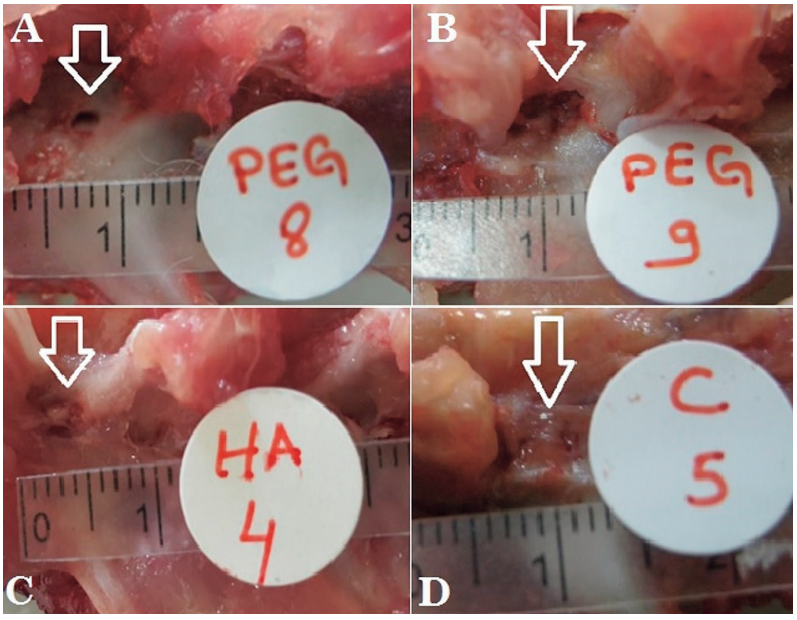

Fig. 2. Appearance of epidural fibrosis levels in the area of hemilaminectomy. A: Anatomical structure intact, no adhesion (Grade 0). **B:** Very thin scar layer and minimal adhesion (Grade 1). **C:** Middle grade scar tissue and adhesion (Grade 2). **D:** Dense and very tight adhesion (Grade 3).

Results

Postoperative complications such as local wound infection and paralysis were not observed in any of the groups (Group I, II, III). No adverse effects of 0.9% NaCl, 5% PEG 4000 and HA used in the experiment were observed.

Macroscopical evaluation

In the hemilaminectomy sites of rabbits treated with 0.9% NaCl (Control group, Group I); severe thickness and tenacious epidural scar adhesions was found between the dura mater and surrounding tissue (in 10 cases Grade 3) (Figure 2D), moderate adhesion and scar tissue (in 1 case Grade 2), and minimal adhesion and very thin scar tissue (in 1 case Grade 1) were observed. In the Group II (5% PEG 4000); dura mater was clean without any evidence of adhesion or scar tissue (in 7 cases Grade 0) (Figure 2A), and minimal adhesions and very thin scar tissue were present (in 5 cases Grade 1) (Figure 2B). In the Group III (HA); moderate adhesion and scar tissue (in 5 cases Grade 2) (Figure 2C), minimal adhesion and very thin scar tissue (in 5 cases Grade 1), in 1 case Grade 0 and in 1 case Grade 3 were observed. Macroscopic evaluation of groups was presented in Table 1.

It was determined that hemilaminectomy size decreased by approximately 1 mm at 8th and 12th week. In two cases, the area of hemilaminectomy was closed by new bone formation.

According to the epidural fibrosis gross score, Group II (5% PEG 4000) was significantly different from Group I ($P < 0.000$) and Group III ($P < 0.002$). Group III (HA) was significantly different from Group I (Control) ($P < 0.001$). The difference between the groups was significant ($P < 0.000$).

Histopathological evaluation

In the hemilaminectomy sites of rabbits treated with 0.9% NaCl (Control group, Group I); it was observed that filled with severe fibrous tissue of the epidural space and the scar tissue adhered to the dura mater and pulled the dura mater and nerve tissues. (Figure 3A, B). In the Group II (5% PEG 4000); minimal fibrotic changes were observed (Figure 4A, B). In the Group III (HA); fewer fibrotic changes were

Table 1. Macroscopic evaluation of groups according to Epidural Fibrosis Gross Score

GROUPS	WEEKS	GRADE 0	GRADE 1	GRADE 2	GRADE 3	Statistical
Group I (Control, n:12)	2nd	–	1	1	1	a,b,d
	4th	–	–	–	3	
	8th	–	–	–	3	
	12th	–	–	–	3	
Group II (5% PEG 4000, n:12)	2nd	1	2	–	–	a,c,d
	4th	2	1	–	–	
	8th	2	1	–	–	
	12th	2	1	–	–	
Group III (HA, n:12)	2nd	–	2	1	–	b,c,d
	4th	–	1	2	–	
	8th	–	1	1	1	
	12th	1	1	1	–	

PEG: Polyethylene Glycol, HA: Hyaluronic acid. a: Group I was significantly different from Group II ($P < 0.000$) b: Group I was significantly different from Group III ($P < 0.001$). c: Group II was significantly different from Group III ($P < 0.002$). d: The difference between the groups was significant ($P < 0.000$).

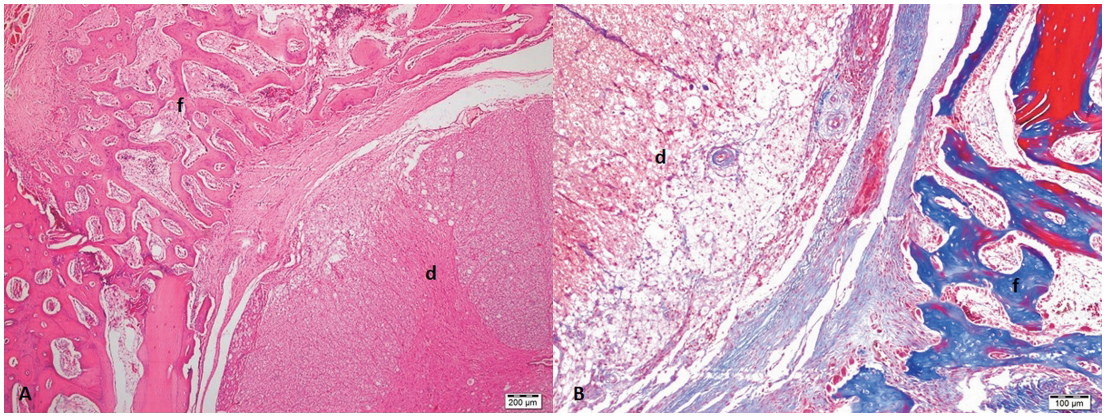

Fig. 3. Photomicrographs of severe fibrosis (epidural adhesion) in the Group I (Control) (in terms of amount of scar tissue: Grade 3). H.E. (A) and Masson trichrome (B). (d: dura meter, f: epidural fibrosis).

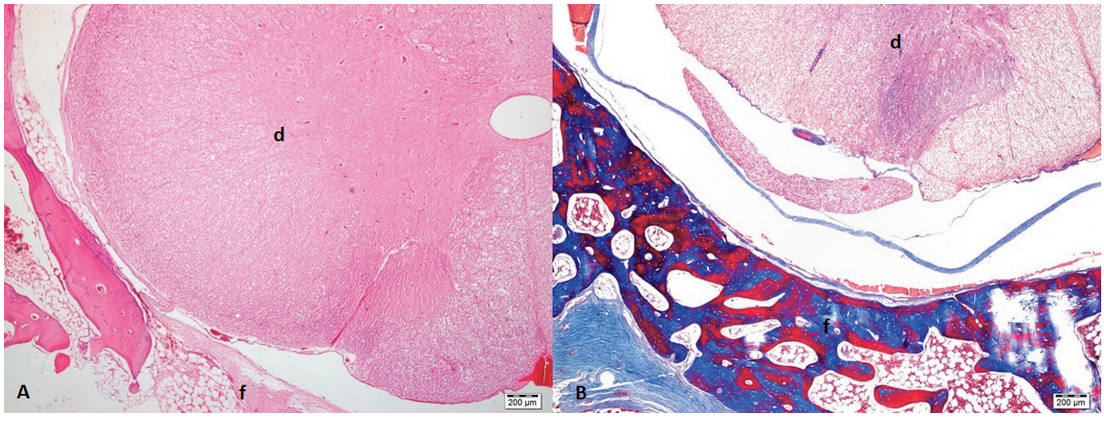

Fig. 4. Photomicrographs of thin fibrosis, no adhesions, duramater free in the Group II (5% PEG 4000) (in terms of amount of scar tissue: Grade 1). H.E. (A) and Masson trichrome (B). (d: dura meter, f: epidural fibrosis).

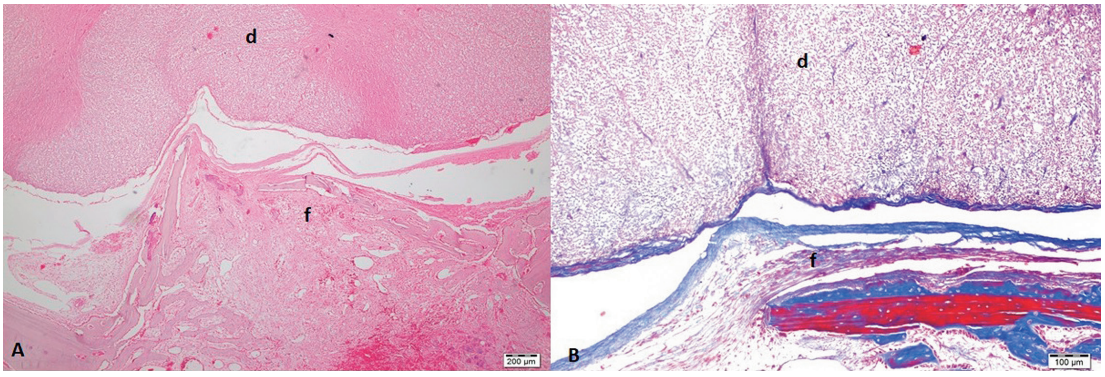

Fig. 5. Photomicrographs of epidural fibrosis in the Group III (HA) (in terms of amount of scar tissue: Grade 2). H.E. (A) and Masson trichrome (B). (d: dura meter, f: epidural fibrosis).

Table 2. Histopathological scoring of epidural scar tissue and adhesions

GROUPS	GRADE 0	GRADE 1	GRADE 2	GRADE 3	Statistical
Group I (Control, n:12)	–	1	2	9	a,b,d
Group II (5% PEG 4000, n:12)	6	4	1	1	a,c,d
Group III (HA, n:12)	1	5	5	1	b,c,d

PEG: Polyethylene Glycol, HA: Hyaluronic acid. a: Group I was significantly different from Group II ($P < 0.000$) b: Group I was significantly different from Group III ($P < 0.001$). c: Group II was significantly different from Group III ($P < 0.034$). d: The difference between the groups was significant ($P < 0.000$).

observed than in the control group (Figure 5A, B). In 5% PEG 4000 group (Group II), the area of hemilaminectomy was closed by new bone formation (two cases).

According to the histopathological scoring of epidural scar tissue and adhesions; in the control group (Group I); presence of only thin fibrous bands between scar tissue and dura matter (in one case Grade 1), continuous adhesions filling less than 2/3 of hemilaminectomy space (in two cases Grade 2) and adhesions filling more than 2/3 the hemilaminectomy space or/and extend to the nerve roots (in 9 cases Grade 3) were detected. In the 5% PEG 4000 group (Group II); dura matter is free of scar tissue (in 7 cases Grade 0), presence of only thin fibrous bands between scar tissue and dura matter (in 4 cases Grade 1) and continuous adhesions filling less than 2/3 of hemilaminectomy space (in one cases Grade 2) were observed. In the HA group (Group III); dura matter is free of scar tissue (in one case Grade 0), presence of only thin fibrous bands between scar tissue and dura matter (in 5 cases Grade 1), continuous adhesions filling less than 2/3 of hemilaminectomy space (in 5 cases Grade 2) and adhesions filling more than 2/3 the hemilaminectomy space or/and extend to the nerve roots (in one case Grade 3) were detected (Table 2).

According to the histopathological scoring of epidural scar tissue and adhesions, 5% PEG 4000 group (Group II) was significantly different from Group I ($P < 0.000$) and Group III ($P < 0.034$). HA group (Group III) was significantly different from control group (Group I) ($P < 0.001$). The difference between the groups was significant ($P < 0.000$).

Discussion

It has been suggested that laminectomy enhances vascular permeability in the cauda equina, vesicular transport in endothelial cells, the increase in vascular permeability may be due to epidural inflammation, and the increase in permeability may increase epidural adhesions[43]. What the place of the scar tissue in the etiology of postoperative pain is not fully understood. Epidural fibrosis not only results with pain but also it results with sensory and motor deficiency in related dermatomes[16]. However, it has been reported that scar tissue made pressure the peripher anatomical structures and enhances the sensitivity of the nerve root the result of limits the movements of the nerve root, as well as the under of the scar tissue is neuronal atrophy and axonal degeneration[21,26,63]. Nerve roots can be pulled and compressed by the contraction of surrounding scar adhesions, affecting axoplasmic transport in nerve fibers, arterial blood supply, and venous drainage[28,64]. In this study, in sections with dense scar tissue, it was observed that the scar tissue adhered to the dura mater and pulled the dura mater and nerve tissues. Similar results have been reported by Bulut *et al*[10].

Osseous regeneration has been determined in the decompression areas (laminectomy and hemilaminectomy) in the majority of experimental studies[5]. Formation of new bone starts from the laminectomy area and osteoblasts are activated[24]. It has been reported that bone regeneration take place at a rate of 50% in 8th weeks and 75% in 12th weeks[18]. In another study has been found a 5–10% reduction in the laminectomy defect at the end of 4th weeks[20]. In this study, hemilaminectomy size decreased by approximately 1 mm at 8th and 12th weeks. In two cases the area of hemilaminectomy were closed by new bone formation. It has also been reported that postoperative scarring may be limited by making the laminectomy defect as small as possible[13]. In clinical practice, it should be known that the decompression area can be closed by new bone formation.

It has been reported that gel and seprafilm forms of hyaluronic acid are more effective than use of hyaluronic acid in prevention epidural fibrozis[26,38,42]. According to the gross score of epidural fibrosis and histopathological scoring of epidural scar tissue, PEG 4000 (5%) was found to be more effective than hyaluronic acid in the prevention of epidural fibrosis.

PEG 4000 is a nontoxic macromolecule[27]. It provides healing without adhesion via covering defective surfaces or by means of a polymer layer. PEG 4000 is keep denatured proteins in traumatized area and enhances its cosolvent activity[4,25,41]. PEG 4000 also changes enzyme activity and enzyme structure and forms a hydrophilic layer around the enzyme[44]. PEG 4000, which has the antibacterial property[45], forms a barrier between the dura meter and the tissues, thereby preventing the formation of epidural fibrosis during the healing process.

Different forms of polyethylene glycol have been used to prevent epidural fibrosis. It has been reported that Silk-Polyethylene Glycol Hydrogels and Mitomycin C-Polyethylene Glycol film combinations reduced the formation of epidural fibrosis[39,62]. Polyethylene Glycol 4000 (5%) has been used for prevention of adhesions after intraabdominal surgeries and tenoraphy[12,27]. This study demonstrated that 5% Polyethylene Glycol 4000 can also be used in the prevention of epidural fibrosis. It is an alternative option to the use of hyaluronic acid both economically and in terms of prevention of epidural fibrosis.

Different mechanical barriers, drugs and methods have been used to prevent epidural fibr osis[1,13,38,49,51,53,56,60,65,67,68]. It was reported that the methodologies used to prevent epidural fibrosis in experimenal studies have mostly been unsatisfactory in their clinical applicability, thus, epidural fibrosis continues to be clinically problem[26]. Satisfactory result has not yet been achieved. Surgical intervention to be applied to remove fibrous tissue is often associated with poor results and newly formed scar tissue. The

goal of treatment is to reduce the incidence of epidural fibrosis[61]. Multiple factors (such as postoperative infection, and hematoma, individual variability in the degree of scar formation, amount of bone removed, laminectomy techniques and anatomic location within vertebral column) are involved important roles in the pathogenesis of epidural fibrosis[30,61]. It is important to know that the individual's wound healing process, the level of traumatization of the tissue, bleeding control, infection and foreign bodies play a role at the scar formation and amount. In this study, severe epidural fibrosis was detected in 9 case in the control group (Group I) despite minimal traumatization of the tissue, bleeding control, and no postoperative infection. In addition to appropriate surgical procedures for the prevention of epidural fibrosis, local or systemic drugs and barriers should be used.

Conclusion

Polyethylene Glycol 4000 (5%) in the prevention of epidural fibrosis encountered as a postoperative complication after hemilaminectomy is an alternative option to the use of hyaluronic acid both economically and in terms of prevention of epidural fibrosis.

Conflict of Interest

Authors have no competing interest.

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