EXPERIMENTAL STUDY

Does dexamethasone therapy affect intimal hyperplasia after injury in rat abdominal aorta models?

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ABSTRACT

BACKGROUND: Intimal hyperplasia is a normal adaptive feature of arteries in response to injuries, which include invasive vascular interventions. Its development limits the long-term success of bypass grafts. Various pharmacological agents have been successfully employed in experimental models to reduce the degree of intimal hyperplasia. In our study, we investigated the efficacy of dexamethasone in reducing intimal hyperplasia in rat abdominal aortas after partial transection and primary repair.

METHODS: In this study, 20 Wistar Albino rats were randomly selected and divided into four groups to compare the effects of low- and high-dose dexamethasone on intima and media thickness compared to the control. Group A (n=5) was the control group, where only skin incision and laparotomy were performed. For Group B (n=5), a median laparotomy was performed, the abdominal aorta was partially transected, and repaired with an 8.0 prolene suture. Doses of 0.1 mg/kg and 0.2 mg/kg dexamethasone were administered in Group C (n=5) and Group D (n=5), respectively. After two weeks, all rats were euthanized, and the repaired abdominal aortas were excised and examined histopathologically. Intima and media thicknesses were measured using the 'Olympus AnalySIS 5' program (Olympus Corporation, Japan) after digital photos were taken.

RESULTS: Based on the measurements, we demonstrated that after transection and repair of the abdominal aorta, the intima/media ratio was not significantly different between the low-dose dexamethasone and non-dexamethasone groups. The intima/media ratio was significantly lower in the high-dose dexamethasone group than in the non-dexamethasone and low-dose dexamethasone groups.

CONCLUSION: After vascular interventions, dexamethasone treatment may reduce intimal hyperplasia and increase patency by providing vascular remodeling.

Keywords: Endothelial injury; dexamethasone; intimal hyperplasia; rat abdominal aorta.

INTRODUCTION

Intimal hyperplasia is a normal adaptive feature of arteries in response to arterial injury, which is an exaggerated response to several forms of arterial injury.[1] All vascular reconstruction procedures cause various degrees of endothelial injury. After injury, there is a complex interaction among smooth muscle cells, adjacent endothelial cells, and blood-borne elements such as platelets and white blood cells, in collagen formation, matrix deposition, and the development of intimal hyperplasia.[2] Denuding the arterial endothelium results in the uncontrolled proliferation of medial myofibroblasts, which migrate

Cite this article as: Canbal Sarılar Ç, Sayın OA, Sarılar M, Bozbuga N, Demir I, Olgac V, Alpagut IU. Does dexamethasone therapy affect intimal hyperplasia after injury in rat abdominal aorta models? Ulus Travma Acil Cerrahi Derg 2024;30:525-530.

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Ulus Travma Acil Cerrahi Derg 2024;30(8):525-530 DOI: 10.14744/tjtes.2024.74411
Submitted: 26.04.2024 Revised: 30.05.2024 Accepted: 20.07.2024 Published: 02.08.2024

across the internal elastic lamina into the intima.[3]

Intimal hyperplasia is a serious clinical problem after invasive vascular interventions as it can lead to occlusion and thrombosis of arteries and bypass grafts.[1] However, the pathophysiology is still unclear. Neointimal hyperplasia limits the long-term success of bypass grafts. Therefore, reducing the hyperplastic response may help improve patency rates of bypass grafts, leading to improved limb salvage and extended life.

Various pharmacological agents have been successfully employed in experimental models to reduce the degree of intimal hyperplasia. These include antithrombotic agents (heparin,[4,5] low molecular weight heparin[5,6]),antiplatelet agents (aspirin,[7] dipyridamole, nonsteroidal anti-inflammatory drugs), antiproliferative agents (anticholinesterase inhibitors,[8-13] colchicine,[14,15]) and anti-inflammatory agents (corticosteroids[16-19]).

White blood cells have been shown to be deposited on the injured vessel wall.[20,21] As such, in our study, we hypothesized that a potential inhibitor of neutrophil function and proliferation, dexamethasone, could have a beneficial effect in decreasing the hyperplastic response. The purpose of this study was to investigate the efficacy of dexamethasone on intimal hyperplasia in the rat abdominal aorta after partial transection and primary repair.

MATERIALS AND METHODS

After receiving approval from the Ethics Committee in 2019 with the number 2019/26, 20 female Wistar albino rats weighing 200-400 g were divided into four groups. They were anesthetized with 50-60 mg/kg of ketamine (Ketalar®) and 5 mg/kg of Xylazine hydrochloride (Rompun®), which were injected intraperitoneally. The rats were placed in the supine position in the operating room. The midline of the abdomen was then shaved. After the operation site was disinfected, a median laparotomy was performed. Animal care complied with the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals, 8th edition (Washington DC: National Academies Press; 2011). The following interventions were performed for each group. Group A (n=5) was the control group, where only a skin incision and laparotomy were performed. For Group B (n=5), after intravenous administration of 100 U/kg of heparin, a median laparotomy was performed, and the infrarenal abdominal aorta was exposed through microdissection. The infrarenal abdominal aorta was clamped with an atraumatic bulldog clamp (Fig. 1), partially transected with an ophthalmic scalpel, and the arteriotomy was repaired with an 8.0 prolene suture. After the preoperative administration of anesthesia and 100 U/kg of intravenous heparin, 0.1 mg/kg and 0.2 mg/kg of dexamethasone were administered by intraperitoneal injection in Group C (n=5) and Group D (n=5), respectively. After partial transection and primary repair of the abdominal aorta in these two groups, dexamethasone was administered daily by intraperitoneal injection for two weeks. All rats were weighed daily. After this period, all rats were humanely euthanized to remove the repaired abdominal aortic segment. The excised repaired aorta was then divided into three parts and placed in 10% buffered formaldehyde (Fig. 2). The aortic specimens were fixed in 10% buffered formalin for three days. After all aortas were collected, five cross-sections from paraffin blocks were prepared following routine tissue tracking for each block. The 3-micron-thick sections obtained from the paraffin blocks were stained with hematoxylin-eosin and elastica-Van-Gieson by a certified histology laboratory (Istanbul University Institute of Oncology Pathology Laboratory). With the Olympus AnalySIS 5 image analysis program (Olympus Corporation, Japan), the intima and media thicknesses were measured by taking the three thickest portions of the artery and averaging the measurements in millimeters.

Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) was used for statistical analysis. The Shapiro-Wilk test was used to analyze descriptive data (mean, standard deviation, median, frequency, rate, minimum, and maximum) as well as the distribution of the data. The Kruskal-Wallis test was used to compare three groups that did not show a normal distribution of quantitative data. The Mann-Whitney U test was to compare two groups. P-values less than 0.01 and 0.05 were regarded as statistically significant.

RESULTS

No deaths occurred after the operation and during the postoperative period. One rat died during anesthesia in Group B and was replaced. At the time of sacrifice, no wound infections or surgical complications were noted. In our study, the excised abdominal aortas were normal in the control group (Fig. 3). In the sections obtained from Group B, the intima layers were irregular and thickened. Elastic tissue staining showed an irregularly thickened lamina elastica interna and loss of continuity (Fig. 4). In Group C, it was observed that rats had thickened aortic intima layers, although there was no irregular papillary thickening. A normal lamina elastica interna was observed in almost all the sections (Fig. 5). In Group D, minimal thickening was detected in the intima layer, while the internal elastic lamina showed no irregularities (Fig. 6). Comparison of the intima/media ratios among the experimental groups revealed statistical significance (p=0.001) (Table 1). Group B showed a significantly higher intima/media ratio compared to Group A (p=0.008) (Table 2). A similar trend was observed when Group C was compared with Group A, with Group C showing a higher intima/media ratio (p=0.008) (Table 2); Group D also had a higher ratio compared to Group A. No difference in the intima/media ratio was noted upon comparison of Groups C and B (p=0.421) (Table 2). Meanwhile, the intima/media ratio was significantly lower in Group D compared to Group B (p=0.008) (Table 2)

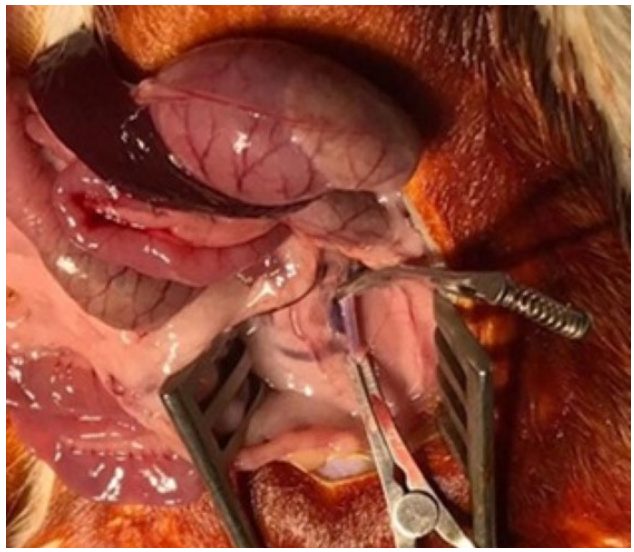

Figure 1. Clamping of the infrarenal abdominal aorta using an atraumatic bulldog clamp.

Figure 2. Removal of the experimental segment of the abdominal aorta.

and also in Group D compared to Group C (p=0.008) (Table 2). With high-dose dexamethasone treatment, weight loss and reduced daily activity did not occur.

DISCUSSION

Intimal hyperplasia is a normal adaptive feature of arteries against hemodynamic stress.[1] All vascular reconstruction procedures cause various degrees of endothelial injury, which can lead to occlusion and thrombosis in the arteries and bypass grafts.[22]

Endarterectomy, balloon angioplasty, and intimal hyperplasia, seen in vascular bypass graft anastomosis regions, are some of the most important factors that lead to the failure of vascular reconstructive interventions over a long period of time.[23] Vascular damage associated with arterial endothelial injury causes uncontrolled proliferation of medial myofibroblasts and migration of myofibroblasts through the internal elastic lamina.[22] The main cause of lumen occlusion in arterial damage models in animals and humans has been shown to be a result of smooth muscle cell proliferation and connective tissue accumulation in the intima.[24] After arterial damage occurs, this area is covered with platelets. After adhesion, the damaged artery releases vasoactive and thrombotic factors (serotonin, adenosine diphosphate, fibrinogen, von Willebrand factor) from the granules of platelets, which also secrete growth factors (platelet-derived growth factors, transforming growth factors, epidermal growth factors). These growth factors, possessing mitogenic properties, initiate smooth muscle cell proliferation.[25] Smooth muscle cells, which begin to multiply in the media layer in response to injury, then migrate to the intima, causing intimal hyperplasia. According to the response-to-injury hypothesis suggested by Russel Ross, the mechanism that initiates intimal thickening depends on a growth factor released from activated platelets and endothe-

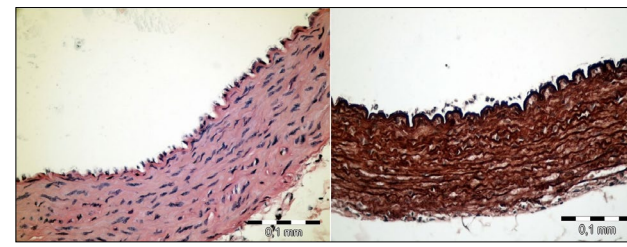

Figure 3. Excised abdominal aorta from the control group.

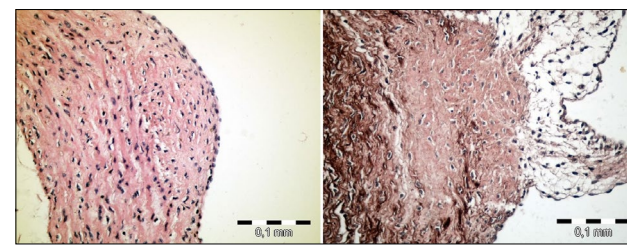

Figure 4. Irregular and thickened intima layers observed in Group B.

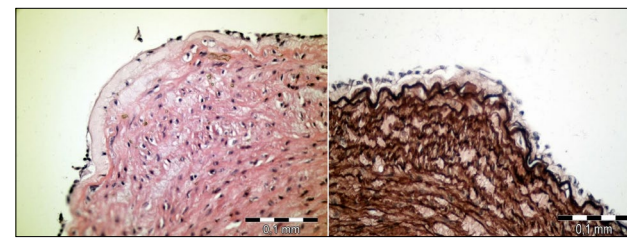

Figure 5. Presence of thickened aortic intima layers in Group C.

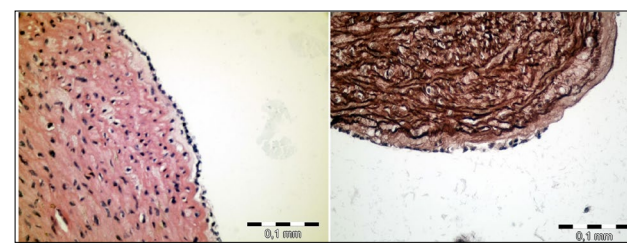

Figure 6. Minimal thickening observed in the intima layer of Group D.

Table 1. Multiple comparison of intima/media ratios across groups

	Group A (n=5)	Group B (n=5)	Group C (n=5)	Group D (n=5)	μp
Intima/Media					
Mean±SD	0.07±0.009	0.81±0.33	0.55±0.10	0.28±0.05	0.001**
Ratio					
Min-Max (Median)	0.07-0.09 (0.08)	0.44-1.29 (0.84)	0.45-0.69 (0.57)	0.23-0.36 (0.27)	

Kruskal-Wallis Test *p<0.05 **p<0.01.

Table 2. Binary comparison of intima/media ratios between groups

Group (n=5)	Group (n=5)	p value
A (control group)	B (only transection group)	0.008 (p<0.05)
A (control group)	C (low dose dexamethasone group)	0.008(p<0.059
A (control group)	D (high dose dexamethasone group)	0.008 (p<0.05)
B (only transection group)	C (low dose dexamethasone group)	0.421 (p>0.05)
B (only transection group)	D (high dose dexamethasone group)	0.008 (p<0.05)
C (low dose dexamethasone group)	D (high dose dexamethasone group)	0.008 (p<0.05)

Mann-Whitney U Test *p<0.05, **p<0.01.

lial cells adhering to the damaged vascular wall, which stimulates the proliferation of smooth muscle cells.[25] Inhibition of the hyperplastic response may significantly prolong vascular patency, reduce organ loss in bypass, and can directly improve survival.[26,27,28] As mentioned, various pharmacological methods have been used to prevent the development of intimal hyperplasia. These include antithrombotic agents (heparin, low molecular weight heparin), antiplatelet agents (aspirin), and antiproliferative agents (corticosteroids).[22] In damaged vessel walls, leukocyte accumulation has been observed. Corticosteroids and immunosuppressive agents are useful in reducing the hyperplastic response in leukocyte function. [29] Dexamethasone is a synthetic glucocorticoid with a wide range of biological effects, including the regulation and suppression of immune functions. It has been shown to inhibit the functions of lymphocytes, fibroblasts, macrophages, and other immune cells. It has also been shown to suppress the growth of tumor cells[30] and inhibit the development of neointimal hyperplasia after balloon injury.[31] Dexamethasone inhibits smooth muscle cell proliferation by inhibiting the phosphorylation of the retinoblastoma (Rb) protein and by halting the cell cycle in the early G1 phase.[32,33] Its potent anti- inflammatory and immunomodulatory actions are due to the inhibition of the activity of transcription factors, such as AP-1 and nuclear factor kappa B (NF-κB), that are involved in the activation of proinflammatory genes.[34]

The molecular mechanism by which glucocorticoids antagonize the biological function of cytokines under NF-κB regulation can be explained in at least two different ways.[35] Several studies have evaluated the effect of dexamethasone on neointimal hyperplasia. Petrik et al. have shown in New Zealand White rabbits that the individual use of enalapril and dexamethasone is more effective than their combined use in reducing the development of intimal hyperplasia.[22] Chervu et al. demonstrated in a study among the carotid arteries of rabbits with balloon catheter-induced damage that dexamethasone and azathioprine reduced intimal hyperplasia. Corticosteroids were beneficial for both vein grafts and prosthetic grafts. High-dose steroids have also been shown to significantly reduce intimal hyperplasia in the model with intrinsic injury by a balloon catheter.[29] Another study found that dexamethasone therapy inhibited smooth muscle cell proliferation and DNA synthesis, depending on the dose. Dexamethasone has been shown to inhibit cell cycle progression from the G1 to S phase.[30]

In our study, we demonstrated that after transection and repair of the abdominal aorta, the intima/media ratio was not significantly different between the low-dose dexamethasone and non-dexamethasone groups. The intima/media ratio was significantly lower in the high-dose dexamethasone group than in the non-dexamethasone and low-dose dexamethasone groups. Systemic dexamethasone has systemic side ef-

fects. It is well known that prolonged systemic dexamethasone therapy frequently leads to altered body fat deposition, muscle atrophy, impaired wound healing, and increased plasma lipid levels. Pires et al. demonstrated that local dexamethasone therapy, such as dexamethasone-eluting stents, had no systemic side effects and that neointimal growth inhibition was almost identical.[36] Local dexamethasone was associated with medial atrophy, reduced vascular smooth muscle cell and collagen content, an increased number of apoptotic cells, and internal elastic lamina fractures. In contrast, a dexamethasone delivery device failed to reduce neointima formation in a porcine model of restenosis.[37] These divergent results might be due to different dexamethasone concentrations or to species-related arterial differences. Thus, in our study, dexamethasone was administered intraperitoneally, and systemic high-dose dexamethasone treatment inhibited neointima formation but was associated with side effects including weight loss and reduced daily activity. The strongly hydrophobic character of the anti-restenotic drugs, such as dexamethasone, can lead to high arterial wall concentrations that exceed the bulk concentration.[38] This highly concentrated local delivery of anti-restenotic agents may lead to increased vessel wall toxicity. In our study, we found a positive correlation between the concentration of dexamethasone used. An increased amount of dexamethasone inhibited neointima proliferation. Neointimal hyperplasia is the major cause of stenosis after vascular interventions and anastomosis. After vascular interventions, dexamethasone treatment may reduce intimal hyperplasia and increase patency by providing vascular remodeling.

CONCLUSION

Dexamethasone therapy may lead to inhibition of neointimal hyperplasia in a rat abdominal aorta model.

Ethics Committee Approval: This study was approved by the Bezmialem Vakıf University Ethics Committee (Date: 28.02.2019, Decision No: 2019/26).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: Ç.C.S., Ö.A.S., M.S.; Design: Ç.C.S., Ö.A.S., M.S.; Supervision: Ç.C.S., N.B., İ.U.A.; Resource: Ç.C.S., Ö.A.S.; Materials: Ç.C.S., Ö.A.S.; Data collection and/or processing: V.O.; Analysis and/or interpretation: N.B.; Literature search: M.S., İ.D., İ.U.A., N.B.; Writing: Ç.C.S.; Critical review: İ.U.A., N.B.

Conflict of Interest: None declared.

Financial Disclosure: The author declared that this study has received no financial support.

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DENEYSEL ÇALIŞMA - *ÖZ*

Parsiyel transekte edilip primer tamir edilen rat abdominal aortlarında deksametazonun intimal hiperplaziye etkisi

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AMAÇ: İntimal hiperplazi arterlerin hemodinamik strese karşı normal adaptif bir özelliği olduğu kadar arteriyel injurilerin iyileşmesinin karakteristik bir özelliğidir.İntimal hiperplazi,invaziv vasküler girişimler için önemli bir klinik problemdir ve bypass greftlerinin uzun dönem sonuçlarını etkiler. İntimal hiperplaziyi azaltmak çeşitli farmakolojik ajanlar deneysel çalışmalarda başarıyla kullanılmaktadır.

GEREÇ VE YÖNTEM: Çalışmamızda parsiyel transekte edilip primer onarılan sıçan abdominal aortlarında deksametazonun intimal hiperplaziye etkisini araştırdık.

Çalışmamızda 20 adet Wistar Albino cinsi rat rastgele 4 gruba ayrıldı. Grup A (Kontrol grubu) (n=5) ratlara laparotomi yapıldı ve abdominal aorta bulundu, dönüldü. Gru Sonuç olarak yüksek doz deksametazonun sıçan abdominal aortlarında intimal hiperplaziyi inhibe edebileceğini söyleyebiliriz. p B'deki ratlara (n=5) laparotomi yapıldı, Abdominal aorta bulundu, dönüldü. Abdominal aorta parsiyel transekte edilip 8.0 prolen ile dikilmiştir. Grup C deki ratlara (n=5) 0.1 mg/kg deksametazon intraperitoneal uygulandı. Laparotomi yapıldı. Abdominal aorta bulundu, dönüldü. Abdominal aorta parsiyel transekte edilip 8.0 prolen dikiş ile dikildi. İşlemden sonra 2 hafta deksametazon tedavisine devam edildi. Grup D'deki ratlara işlem öncesi 0.2 mg/kg deksametazon intraperitoneal uygulandı. Abdominal aorta bulundu, dönüldü. Abdominal aorta parsiyel transekte edilip 8.0 prolen dikiş ile dikildi. İşlemden sonra 2 hafta deksametazon tedavisine devam edildi. Tüm sıçanlar 2 hafta sonra sakrifiye edildikten sonra primer onarılan abdominal aortlar eksize edildi ve histopatolojik olarak incelendi.

BULGULAR: İncelemeler sırasında çekilen dijital fotoğraflar üzerinden "Olympus analySİS 5" görüntü analiz programı ile intima ve media kalınlıkları mm cinsinden ölçülerek intimal ve medial alan hesaplanarak intima/media oranı kontrol grubu ile karşılaştırılarak incelenecektir. Abdominal aort transeksiyonu ve onarımı sonrası düşük doz deksametazon ve deksametazon verilmeyen grupların intima/media oranları kıyaslandığında istatiksel olarak anlamlı değildir. Yüksek doz deksametazon verilen grupta deksametazon verilmeyen ve düşük doz deksametazon verilen gruplara göre intima/media oranları istatiksel olarak daha düşük bulunmuştur.

SONUÇ: Sonuç olarak yüksek doz deksametazonun sıçan abdominal aortlarında intimal hiperplaziyi inhibe edebileceğini söyleyebiliriz..

Anahtar sözcükler: intimal hiperplazi, endotel hasarı, sıçan abdominal aorta, deksametazon

Ulus Travma Acil Cerrahi Derg 2024;30(8):525-530 DOI: 10.14744/tjtes.2024.74411