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Impact of sympathetic denervation via paraaortic lymphadenectomy on blood pressure in endometrial cancer patients

Paraaortik lenfadenektomi ile sempatik denervasyonun kan basıncı üzerine etkisi

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Abstract

Objective: To evaluate the effect of para-aortic lymphadenectomy on blood pressure changes in endometrial cancer patients.

Materials and Methods: This retrospective study included patients with endometrial cancer treated surgically between 2017 and 2023. Patients undergoing para-aortic lymphadenectomy, up to the renal artery, in a non-nerve-sparing fashion, were compared with those undergoing pelvic lymphadenectomy or sentinel lymph node mapping. Data collected included age, body mass index, comorbidities including hypertension, diabetes mellitus, coronary artery disease, operative time, number of lymph nodes removed, tumor size, and postoperative complications. Preoperative blood pressure was recorded during outpatient visits, and postoperative measurements were collected daily during hospitalization and at follow-up visits. Statistical analyses assessed differences in systolic and diastolic blood pressure changes, operative outcomes, and complications.

Results: A total of 264 patients were analyzed. Patients in the para-aortic group had significantly longer operative times. Tumor size was larger in the para-aortic group than in another group. Systolic blood pressure decreased significantly in the para-aortic group compared to the control group (para-aortic: -17 mmHg *vs.* non-para-aortic: -1.10 mmHg, $p<0.05$), with a similar trend for diastolic pressure (-8.00 mmHg *vs.* -0.80 mmHg, $p<0.05$). Chylous ascites (15.6% *vs.* 5.6%) and ileus (0% *vs.* 12%) were more common in the para-aortic group, along with the administration of radiotherapy and chemotherapy. Both systolic and diastolic blood pressures were significantly lower in paraaortic group, in both early and late postoperative follow-up measures ($p<0.005$).

Conclusion: Aortic lymphadenectomy is associated with decreased blood pressure and may have therapeutic potential for hypertensive patients, highlighting the need for prospective randomized studies to explore this effect further.

Keywords: Cancer of endometrium, hypertension, lymph node excison

Öz

Amaç: Bu çalışmanın amacı sinir koruyucu olmayan paraaortik lenfadenektominin paraaortik ve renal bölgedeki sempatik sinir liflerini etkileyerek kan basıncı üzerindeki değişimlerini değerlendirmektir.

PRECIS: We evaluated the impact of para-aortic lymphadenectomy on blood pressure levels in endometrial cancer patients, demonstrating significant reductions linked to sympathetic nerve disruption.

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Gereç ve Yöntemler: Bu retrospektif çalışma, 2017-2023 yılları arasında cerrahi tedavi uygulanan endometrium kanseri hastalarını içermektedir. Renal arter seviyesine kadar sinir koruyucu olmayan paraaortik lenfadenektomi yapılan hastalar, pelvik lenfadenektomi veya sentinel lenf nodu haritalaması yapılan hastalarla karşılaştırılmıştır. Toplanan veriler arasında yaş, vücut kitle indeksi, hipertansiyon, diyabet, koroner arter hastalığı gibi komorbiditeler, operasyon süresi, çıkarılan lenf nodu sayısı, tümör boyutu ve postoperatif komplikasyonlar yer almaktadır. Preoperatif kan basıncı ölçümleri ameliyat öncesi poliklinik değerlendirmesinde, postoperatif ölçümler ise hastanede yatış süresince ve onkolojik takip sırasında kaydedilmiştir. Kan basıncı değişimleri, operasyon sonuçları ve komplikasyonlar arasındaki farklar istatistiksel olarak analiz edilmiştir.

Bulgular: Toplam 264 hasta çalışmaya dahil edilmiştir. Paraaortik grupta operasyon süresi daha uzun ve tümör boyutları daha büyük bulunmuştur. Sistolik kan basıncı paraaortik grupta kontrol grubuna kıyasla anlamlı olarak daha fazla düşmüştür (-17 mmHg *vs.* -1,10 mmHg, p<0,05). Benzer şekilde, diyastolik kan basıncı da paraaortik grupta daha fazla düşmüştür (-8,00 mmHg *vs.* -0,80 mmHg, p<0,05). Şilöz asit (%15,6 *vs.* %5,6), ileus (%12 *vs.* %0) ve adjuvan radyoterapi/kemoterapi uygulaması paraaortik grupta daha sık gözlenmiştir. Postoperatif erken dönemde ve uzun vadeli takiplerde sistolik ve diyastolik kan basınçlarındaki düşüşler anlamlı şekilde korunmuştur (p<0,005).

Sonuç: Paraaortik lenfadenektomi, sistolik ve diastolik kan basınçlarında anlamlı düşüşlerle ilişkilidir ve hipertansif hastalar için tedavi edici potansiyele sahip olabilir.

Anahtar Kelimeler: Endometriyum kanseri, hipertansiyon, lenf nodu diseksiyonu

Introduction

Hypertension is a common condition in the general population and a significant cause of morbidity, particularly among older adults[1]. In patients with endometrial cancer, hypertension is a frequently associated comorbidity, observed both in the presence and absence of obesity[2]. While obesity is a well-known risk factor for hypertension, the coexistence of metabolic syndrome further increases the prevalence of both hypertension and endometrial cancer[2]. This suggests that metabolic factors may create a common underlying pathway between these two conditions.

Hypertension is a major comorbidity among patients with endometrial cancer, with approximately 40% of these patients requiring antihypertensive medication[3,4]. The most common type of hypertension is essential hypertension and underlying factors include genetic factors, age, lifestyle factors and stress[5]. Initial treatment strategies typically involve dietary modifications and antihypertensive medications[5]. Numerous studies have demonstrated the involvement of the adrenergic system in blood pressure regulation. Blocking this system is a fundamental mechanism underlying antihypertensive therapy[6]. However, sympathetic fibers located in the paraaortic region, particularly in the perirenal area, have been implicated as a potential cause of hypertension by increasing sodium uptake, renin secretion, and renal arterial vasoconstriction[7]. Based on this knowledge, angiographic radiofrequency ablation has been explored as a treatment option for patients unresponsive to antihypertensive therapies[8]. Studies have reported that this method can lead to an average reduction in blood pressure by approximately 20 mmHg. In some cases, patients no longer required antihypertensive medications[9]. The majority of the studies accumulated after 2020. In patients with endometrial cancer, especially in those at higher risk, retroperitoneal lymphadenectomy is a standard component of surgical management when sentinel lymph node mapping is not available. The cranial boundary of the lymphadenectomy is typically defined at the level of the renal artery. While nerve-sparing approaches exist, periaortic neural structures within the lymphatic tissue are often excised or damaged during systematic lymphadenectomy.

This study is based on the following hypothesis: if blocking neural structures in the para-aortic region can lead to a reduction in blood pressure, it is plausible that para-aortic lymphadenectomy in endometrial cancer patients, may similarly result in decreased postoperative blood pressure levels. Our aim was to evaluate the changes in blood pressure measurements between the preoperative and postoperative periods in patients undergoing para-aortic lymphadenectomy up to the level of the renal arteries.

Materials and Methods

Our study received approval from the Institutional Review Board (İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital, Non-Interventional Research Ethics Committee - no: 2023/211, date: 27.12.2023). The study had been reviewed by the appropriate ethics committee and had been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000. Patients treated for endometrial cancer were identified through the hospital database. The records of patients who underwent surgery between 2017 and 2023 were reviewed. A total of 289 patients with endometrial cancer were initially included in the study. Seven patients who underwent bulky lymph node dissection for cytoreduction in advanced-stage endometrial cancer, and ten patients who underwent para-aortic lymphadenectomy up to the level of the inferior mesenteric artery were excluded from the study. Additionally, eight patients with missing postoperative blood pressure monitoring data were excluded. Figure 1 shows the flowchart of the study. Data collected from patient files included age, gravida, parity, history of previous surgeries, presence of diabetes, coronary artery disease, body mass index, endometrial biopsy results, findings from preoperative imaging studies, pelvic lymphadenectomy, and paraaortic lymphadenectomy. Additionally, those with conditions affecting blood pressure, such as bleeding, hypovolemia, and arrhythmia were excluded from the study. All persons gave their informed consent prior to their inclusion in the study.

The study group comprised patients with endometrial cancer who underwent para-aortic lymphadenectomy up to the level of the renal vein via either laparoscopic transperitoneal, extraperitoneal, or laparotomy approaches. Patients who did not undergo lymphadenectomy; and who underwent pelvic lymphadenectomy, pelvic lymph node sampling, or sentinel lymph node mapping were included in the control group. Preoperative blood pressure measurements were taken during outpatient visits, which typically occurred two weeks prior to surgery. Blood pressure measurements were taken under ideal conditions, with patients seated comfortably in a quiet environment, their back supported, legs uncrossed, and arms at heart level. A properly calibrated and validated blood pressure monitor was used, and measurements were obtained after a 5-minute rest period, avoiding recent physical activity, caffeine, or smoking. Postoperative blood pressure readings were collected daily from the hospital system. On the first postoperative day, measurements were taken hourly, while on subsequent days, they were recorded every six hours unless an unusual situation arose. The daily postoperative blood pressure values reported in our analysis was presented as the average of all measurements taken throughout each day. Patients' blood pressure data were collected throughout their hospitalisation and at follow-up outpatient clinic visits.

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Comparisons between groups for normally distributed continuous variables were performed using the independent samples t-test, while the Mann-Whitney U test was used for variables without normal distribution. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. The mean differences in systolic and diastolic blood pressure changes between the groups were calculated, and their effect sizes were assessed using Cohen's d. Effect sizes were interpreted as small (0.2), medium (0.5), or large (0.8), based on Cohen's criteria. A p-value of <0.05 was considered statistically significant.

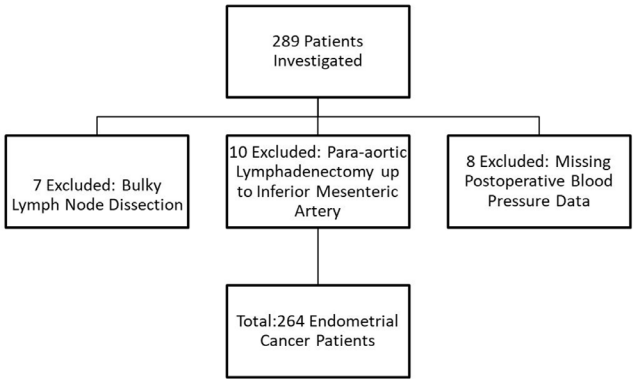

Figure 1. Patient selection process for the study, showing exclusions and final cohort of 264 patients

Results

The mean age of the patients was similar between the groups (61±12 *vs.* 62±10 years, p=0.528), and there was no significant difference in terms of gravida, platelet count or CA-125 levels (p>0.05).

The operation time was longer in paraaortic group (4±1 *vs.* 3±1 hours, p<0.001) and a greater number of pelvic lymph nodes removed (39±17 *vs.* 21±20, p<0.001) as well as number paraaortic lymph nodes collected (42±24 *vs.* 0±0, p<0.001). Tumor size at final pathology was larger in the paraaortic group (4±2 *vs.* 3±2, p<0.001), and hospital stays were longer (p<0.001).

Suspicious lymph nodes were more frequent in the paraaortic group (22.9% *vs.* 9.7%, p=0.016). Additionally, the paraaortic group had significantly higher rates of radiotherapy (65.6% *vs.* 31.9%, p<0.001); chemotherapy (36.5% *vs.* 11.1%, p<0.001). While overall complications like evisceration were not significantly different, chylous ascites was more frequent in the paraaortic group (15.6% *vs.* 5.6%, p=0.030). Similarly, ileus was more frequent in the paraaortic group. Demographic and clinical characteristics of the patients were given in Table 1 and Table 2.

Blood pressure changes were significantly greater in the paraaortic group, with systolic blood pressure showing a mean change of -17.20 compared to -1.10 in the no paraaortic group (p<0.001, Cohen's d=3.52); and diastolic blood pressure a mean change of -8.00 compared to -0.80 (p<0.001, Cohen's d=2.89). These findings indicate that paraaortic lymphadenectomy is associated with longer operative times, greater lymph node

Table 1. Demographic and laboratory parameters of patients underwent paraaortic lymphadenectomy and no paraaortic lymphadenectomy

	No paraaortic (n=72)	Paraaortic (n=192)	p-value
Age	61±12	62±10	0.528
Gravida	2 (0-12)	2 (0-8)	0.916
BMI	33±7	32±6	0.167
Plt	288±71	298±83	0.358
CA-125	32±70	63±304	0.393
Preop tumor size	3±2	4±6	0.055
Op. time	3±1	4±1	0.000
Pelvic LN	21±20	39±17	0.000
Paraaortic LN	0±0	42±24	0.000
Tumor size	3±2	4±2	0.000
Hospital stay	5 (2-31)	9 (2-65)	0.000

BMI: Body mass index, Plt: Platelet, Op.: Operation, LN: Lymph node

dissection, higher utilization of adjuvant therapies, significant changes in blood pressure, and an increased risk of developing chylous ascites (Table 3).

For systolic blood pressure, the paraaortic group showed a greater reduction compared to the no paraaortic group throughout the 10 days, as depicted by the downward trend in the blue line in Figure 1. The mean systolic blood pressure in the no paraaortic group remained relatively stable around the preoperative mean, while the paraaortic group showed significant decreases. These differences reflect the earlier reported mean changes (-1.10 *vs.* -17.20, p<0.001, Cohen's d=3.52).

Similarly, the diastolic blood pressure graph indicates a more prominent reduction in the paraaortic group compared to the no paraaortic group, consistent with the reported mean changes (-0.80 *vs.* -8.00, p<0.001, Cohen's d=2.89). The preoperative mean diastolic pressure is marked as a reference, and the trends show that the paraaortic group deviates significantly from this baseline over time. Figure 2 and Figure 3 showed blood pressure changes over time.

Table 2. Comorbidities and postoperative complications in paraaortic and no paraaortic lymphadenectomy groups

	No paraaortic (n=72)	Paraaortic (n=192)	p-value
Hypertension			
No	30 (41.7%)	68 (35.4%)	**0.349**
Yes	42 (58.3%)	124 (64.6%)	
Diabetes mellitus			
No	50 (69.4%)	128 (66.7%)	**0.668**
Yes	22 (30.6%)	64 (33.3%)	
Suspicious lymph node			
No	65 (90.3%)	148 (77.1%)	**0.016**
Yes	7 (9.7%)	44 (22.9%)	
Radiotherapy			
No	49 (68.1%)	66 (34.4%)	**0.000**
Yes	23 (31.9%)	126 (65.6%)	
Chemotherapy			
No	64 (88.9%)	122 (63.5%)	**0.000**
Yes	8 (11.1%)	70 (36.5%)	
Evisceration			
No	72 (100%)	187 (97.4%)	**0.167**
Yes	0 (0.0%)	5 (2.6%)	
Ileus			
No	72 (100%)	186 (93.8%)	**0.001**
Yes	0 (0.0%)	12 (6.2%)	
Chylous ascites			
No	68 (94.4%)	162 (84.4%)	**0.030**
Yes	4 (5.6%)	30 (15.6%)	

Table 3. The comparison of sistolic and diastolic blood changes in paraaortic and no paraaortic groups

	No paraaortic	Paraaortic	Mann-Whitney U statistic	Cohen's d
Systolic change	-1.10	-17.20	p<0.001	3.52
Diastolic change	-0.80	-8.00	p<0.001	2.89

Discussion

This study demonstrates that para-aortic lymphadenectomy, performed up to the level of the renal artery in patients with endometrial cancer, is associated with a significant reduction in postoperative blood pressure levels. The findings align with existing evidence on the role of neural structures within the para-aortic region in blood pressure regulation. Extending lymphadenectomy to include the para-aortic area may disrupt sympathetic fibers that contribute to renal vasoconstriction, sodium uptake, and renin secretion, thereby reducing blood

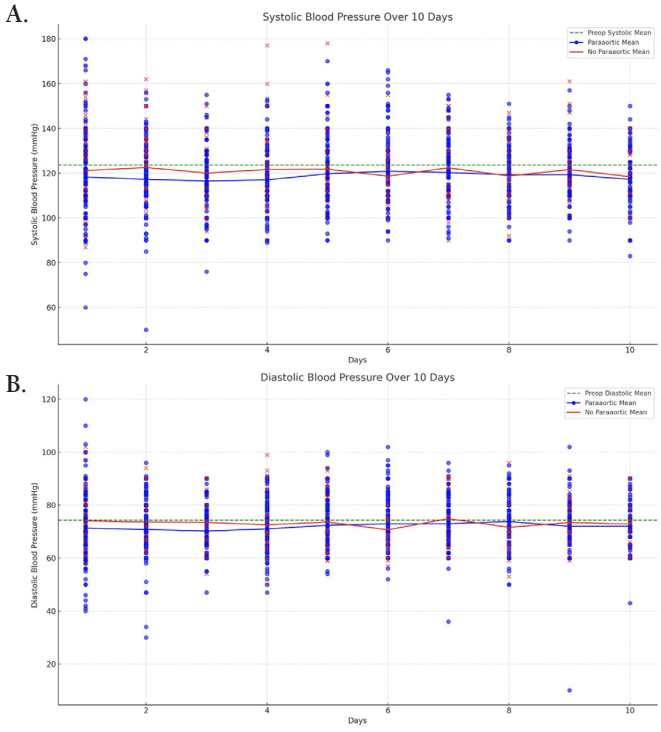

Figure 2. A. Systolic blood pressure trends over 10 days in patients undergoing para-aortic lymphadenectomy compared to controls. Preoperative systolic blood pressure levels are indicated by the green dashed line, **B.** Diastolic blood pressure trends over 10 days for the same groups, showing a similar pattern to systolic pressure. Preoperative diastolic levels are marked with a green dashed line

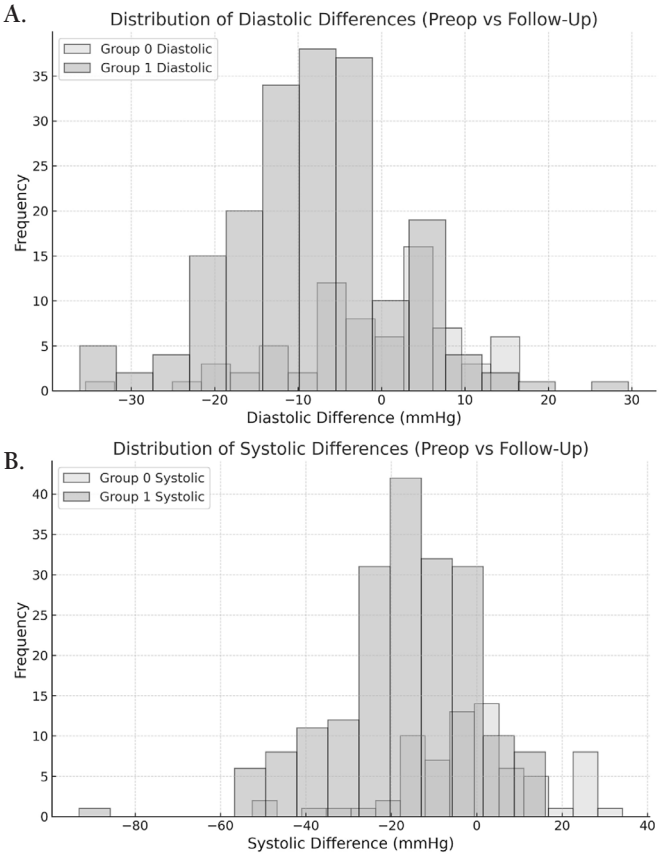

Figure 3. A. Distribution of diastolic blood pressure differences (preoperative *vs.* follow-up) in patients undergoing para-aortic lymphadenectomy and controls, **B.** Distribution of systolic blood pressure differences (preoperative *vs.* follow-up) in the same groups, highlighting significant reductions in the para-aortic group

pressure. These results are consistent with prior studies evaluating interventions such as renal sympathetic denervation, which have similarly shown significant blood pressure reductions through targeted disruption of neural pathways.

The aorticorenal splanchnic nerves are constituted by the least and lesser splanchnic nerves, which play a critical role in regulating renal vascular tone and renin secretion[10]. Sympathetic activation via these nerves induces renal vasoconstriction, reducing blood flow and glomerular filtration rate to maintain systemic hemodynamic stability. Additionally, their adrenergic signaling stimulates renin release, activating the renin-angiotensin-aldosterone system to support blood pressure and fluid balance[11]. The sympathetic nerves give fibers to the renal plexus and reach the kidney, traversing the renal artery. Renal denervation has emerged as a promising interventional therapy for hypertension, targeting the renal sympathetic nervous system to achieve blood pressure reduction. This procedure disrupts sympathetic efferent and sensory afferent fibers, reducing renin secretion, sodium reabsorption, and systemic sympathetic outflow, which collectively contribute to regulation[12]. Similar mechanisms may explain blood pressure reductions observed following para-aortic lymphadenectomy, where the renal nerves could usually be affected due to their anatomical proximity to the para-aortic lymphatic structures. Evidence from experimental studies indicates that ablative or inhibitory interventions targeting renal nerves can significantly alter sympathetic activity, suggesting that such surgical approaches could share mechanistic similarities with renal denervation procedures in modulating blood pressure[13,14].

We observed in our study a significant reduction in blood pressure following paraaortic lymphadenectomy, with systolic blood pressure showing a mean decrease of 17.20 mmHg in the paraaortic group. This reduction exceeds the systolic blood pressure decrease of approximately 13 mmHg reported in renal denervation studies[15], which involve angiographic ablation of sympathetic nerves as a treatment for resistant hypertension. While renal denervation has been widely studied, with long-term follow-up data demonstrating sustained blood pressure reductions, there is currently no comparable data in the literature to show the impact of paraaortic lymphadenectomy on blood pressure changes. The lack of studies exploring the disruption of sympathetic nerves during paraaortic lymphadenectomy and its effects on blood pressure highlights the originality of our findings. This suggests that surgical interruption of sympathetic pathways during lymphadenectomy may play a role in postoperative blood pressure regulation, offering a new area for future research.

The findings from the study conducted Wen et al.[16] highlight the potential adverse effects of para-aortic lymphadenectomy, particularly in non-nerve-sparing procedures. Complications such as lymphorrhea, lymphocele, and acute intestinal obstruction were observed more frequently in the para-aortic group compared to the nerve sparing para-aortic lymphadenectomy group, consistent with our study's findings of increased rates of ileus, chylous ascites, and longer hospital stays in the para-aortic lymphadenectomy cohort. Despite these complications, our study revealed a significant reduction in systolic blood pressure following para-aortic lymphadenectomy. These results indicate a dual perspective: while para-aortic lymphadenectomy carries a risk of postoperative complications, it also offers a potential therapeutic benefit for hypertension management.

In our study, significant reductions in both systolic and diastolic blood pressure were observed following para-aortic lymphadenectomy, with consistent effects seen in both short-term and long-term follow-ups. The changes in blood pressure align with findings from renal denervation studies, where sustained systolic blood pressure reductions of approximately 12.7 mmHg were reported over 36 months, and similar long-term decreases were observed over 10 years[17]. However, the magnitude of blood pressure reduction in our study, particularly during the early postoperative period, was more pronounced, with systolic blood pressure showing a median decrease of approximately 17 mmHg. This suggests that the

surgical disruption of para-aortic sympathetic nerves during lymphadenectomy may result in both immediate and sustained antihypertensive effects. While renal denervation has been widely studied as a therapy for resistant hypertension, our findings highlight a potential additional benefit of para-aortic lymphadenectomy in reducing blood pressure.

Study Limitations

The limitation of the study is it's retrospective design inherently introduces potential biases and limits the ability to establish causal relationships. The variability in follow-up periods among patients may have influenced the consistency of the results. Additionally, the absence of ambulatory blood pressure monitoring, such as Holter measurements, restricts the ability to evaluate more detailed fluctuations and patterns in blood pressure changes over time. However, the study also has notable strengths. The inclusion of a strictly defined cohort of patients who underwent para-aortic lymphadenectomy up to the renal vein level ensures a high degree of consistency in the surgical approach. This uniformity strengthens the validity of the observed blood pressure changes as an independent effect of para-aortic lymphadenectomy on the sympathetic nerves, enhancing the reliability of the findings in demonstrating the direct impact of the procedure on blood pressure regulation

Conclusion

Para-aortic lymphadenectomy has a blood pressure-lowering effect and may reduce the need for antihypertensive medication in hypertensive patients.

Ethics

Ethics Committee Approval: Our study received approval from the Institutional Review Board (İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital, Non-Interventional Research Ethics Committee - no: 2023/211, date: 27.12.2023).
Informed Consent: All persons gave their informed consent prior to their inclusion in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.E., B.Ö., C.A., İ.Ç., Concept: S.E., S.Ö., U.A., C.A., H.A.A., T.B.B., İ.Ç., Design: S.E., S.C.İ., S.Ö., B.Ö., U.A., T.B.B., Data Collection or Processing: S.C.İ., U.A., H.A.A., T.B.B., İ.Ç., Analysis or Interpretation: S.E., S.C.İ., S.Ö., B.Ö., H.A.A., İ.Ç., Literature Search: S.E., B.B., Writing: S.E., S.Ö., C.A.
Conflict of Interest: No conflict of interest was declared by the authors.
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