Ankara Üniversitesi Tıp Fakültesi Mecmuası 2012, 65 (1)
DOI: 10.1501/Tıpfak_000000809

CERRAHİ BİLİMLER/*SURGICAL SCIENCES*
Araştırma Makale / Research Article

Per-Operative Levosimendan Use In High-Risk Patients Undergoing Coronary Artery Bypass Surgery

Yüksek Riskle Koroner Arter Cerrahisi Uygulanan Hastalarda Per-Operatif Levosimendan Kullanımı

Ulaş Kumbasar[1], Ali Can Hatemi[1], Mustafa Canikoğlu[1], Aybala Tongut[1], Mete Gürsoy[1], Kadir Çeviker[1], İlhan Özgöl[1], Murat Başkurt[2], Cem Bostan[2], Kamil Karaoğlu[3]

[1] Istanbul University, Institute of Cardiology, Department of Cardiovascular Surgery
[2] Istanbul University, Institute of Cardiology, Department of Cardiology
[3] Istanbul University, Institute of Cardiology, Department of Anesthesiology and Reanimation

Aim: Although conventional inotropic drugs are well examined for myocardial support during weaning from cardiopulmonary bypass (CPB), there is limited experience about a new calcium sensitiser drug, levosimendan. We aimed to investigate effects of early infusion of 'levosimendan' started per-operatively without a loading dose, on outcomes of patients experiencing difficultly to wean from CPB after coronary artery bypass grafting (CABG).

Material and Methods: Forty two consecutive patients undergoing CABG with high Euroscores (>6) were included in the study. Patients received levosimendan at a rate of 0.1 mcg/kg/min (without a loading dose) per-operatively for 24 h. All patients also received dopamine (5-15 mcg/kg/min), 39 patients adrenaline (0.03-0.2 mg/kg/min) and 9 patients were additionally administered dobutamine (6-20 mcg/kg/min). Intra-aortic balloon pump was implanted to four patients who failed to wean from CPB. Pre- and post-operative demographic, echocardiographic and hemodynamic parameters, as well as operative data were analysed.

Results: Mean patient age was 61.36±9.1 years (min:39, max:77). Mean extubation time of patients was 18.34±6.2 hours (min:9, max:34) and mean surgical intensive care unit stay was 5.45±2.3 days (min:1, max:15). In comparison to the pre-operative measurements patients showed statistically significant increase of left ventricle ejection fraction (LVEF) and decrease of left atrial, left ventricular end diastolic and right ventricular end diastolic diameters following levosimendan administration in the post-operative period. Increase of pro-BNP level on the 3rd postoperative day was also statistically significant (p=0.047). However, pro-BNP levels on the post-operative 6th month was not significantly different from pre-operative levels (p=0.4). Heart rate and invasive systolic and diastolic blood pressure levels were recorded at 23rd hour of perfusion and compared with those of 1 hour after its cessation. Although heart rate remains almost constant (p=0.13), increase in systolic and diastolic blood pressures was markedly statistically significant (p=0.0001).

Conclusion: Levosimendan appears to be an efficient drug if used in addition to conventional inotropics for the management of low cardiac output syndrome states before, during or after on-pump cardiac surgery.

Keywords: ***Coronary Artery Bypass Grafting, Low cardiac output, Levosimendan, Cardioprotective Agents, Euroscore.***

Amaç: Kardiyopulmoner bypass (KPB) desteğinin sonlandırılması sırasında miyokardın desteklenmesi için konvansiyonel inotropik ajanlar birçok çalışmada incelendiği halde yeni ve kalsiyum duyarlılığını arttırarak etki gösteren levosimendan hakkında çalışmalar sınırlıdır. Bu çalışmada, koroner arter bypass cerrahisi (KABC) uygulanan ve KPB'den çıkışta zorlanan hastalarda per-operatif dönemde yükleme dozu yapılmadan başlanan levosimendanın etkinliği araştırıldı.

Materyal ve Method: KABC uygulanan ve yüksek Euroscore'a (>6) sahip 42 hasta çalışmaya alındı. Hastalara yükleme dozu olmadan, per-operatif dönemde 24 saat boyunca 0.1 mcg/kg/dk hızında intravenöz yolla levosimendan uygulandı. İlaveten tüm hastalara dopamin (5-15 mcg/kg/dk), 39 hastaya adrenalin (0.03-0.2 mcg/kg/dk) ve 9 hastaya da dobutamin (6-20 mcg/kg/dk) infüzyonu uygulandı. KPB'den ayrılamayan 4 hastaya intraaortik balon pompası (İABP) uygulandı. Pre ve post-operatif demografik özellikler, ekokardiyografik ve hemodinamik parametreler ve operatif veriler analiz edildi.

Sonuçlar: Ortalama hasta yaşı 61.36±9.1 (min:39, maks:77) idi. Ortalama ekstübasyon zamanı 18.34±6.2 saat (min:9, maks:34), ortalama yoğun bakımda kalış süresi 5.45±2.3 gün (min:1, maks:15) olarak hesaplandı. Pre-operatif ölçümlerle karşılaştırıldığında, levosimendan kullanımını takiben post-operatif dönemde hastalarda istatistiksel olarak anlamlı olacak şekilde sol ventrikül ejeksiyon fraksiyonunda (LVEF) artma, sol atriyum (LA), sol ventrikül (LV) ve sağ ventrikül (RV) diyastol sonu çaplarında küçülme saptandı. Pro-BNP seviyesindeki post-operatif 3. gün görülen artış da anlamlı bulundu. Ancak, postoperatif 6. aydaki pro-BNP seviyeleri pre-operatif seviyelerden farklı bulunmadı. Kalp hızı ile sistolik ve diyasyolik kan basınçları perfüzyonun 23. saatinde ve perfüzyon kesildikten 1 saat sonra kaydedildi. Kalp hızı sabit kaldığı halde kan basınçlarında anlamlı artış meydana geldi.

Sonuç: Kardiyopulmoner bypass uygulanarak yapılan koroner arter cerrahisinde, özellikle düşük kardiyak debili hastalarda levosimendan konvansiyonel inotroplarla birlikte kullanıldığında etkili bir ilaç olarak görülmektedir.

Anahtar Kelimeler: Koroner arter bypass cerrahisi, Düşük kardiyak debi, Kardiprotektif ilaçlar, Euroscore

Received : 31.05.2012 • Accepted: 05.06.2012

Correspoding Author

Uz.Dr.Ulaş Kumbasar
GSM : 0 533 357 10 75
E-mail Adress : ulaskumbasar@gmail.com
Adress : İstanbul Instutite of Cardiology

Circulatory support due to post-cardiotomy cardiogenic shock occurs in 1% of patients undergoing cardiac surgery. Patients, especially who had poor left ventricular function need more inotropic support following cardiopulmonary bypass often (1). Commonly used inotropic drugs (adrenalin, dopamine, dobutamine, noradrenalin, milrinone etc.) increase myocardial contractility. However, they also aggravate oxygen need of the myocardium, which in turn creates risk for ischemia and arhythmia (2). The risk may cause further traumatization of the myocardium in patients with an ischemic myocardium. Though, the need for alternative pharmacologic agents is essential, especially for those patients who do not respond to commonly used drugs while weaning from cardiopulmonary bypass (CPB). Levosimendan (Simdax; Orion, Espoo, Finland) increases affinity of contractile proteins to calcium concentrations by binding to cardiac troponin C in a calcium-dependent manner. While levosimendan increases contractile strength, it does not adversely influence ventricular relaxation and it does not cause a significant increase in myocardial oxygen consumption (3-5). Use of levosimendan, which may be considered a new agent, was started around 90's with animal experiments (6-9). In the early 2000's, use of levosimendan increasingly became widespread and introduced into routine practice in recent years (10, 11). The aim of this study was to determine the mid and long-term outcomes of pre-operative levosimendan administration in high-risk patients who had undergone coronary artery bypass surgery (CABG).

Material and Methods

Between 2006 and 2008, 60 patients who had high risk scores (Euroscore >6), low left ventricular ejection fractions (EF<45%) and who subsequently experienced difficulty in weaning from extracorporeal circulation (ECC) despite administration of traditional inotropic support were operated at our institution and 42 of them who were operated for treatment of coronary artery disease were included in the study following local ethics committee approval (12). All patients received continuous infusion of 0,1 mcg/kg/min levosimendan started during ECC without any pre-operative loading dose.

Examined variables included; age, weight, gender, history of diabetes, hypertension, hypercholesterolemia, documented chronic obstructive pulmonary disease, prior myocardial infarction, hepatic and renal functions, previous cardiac interventions (surgery or stent implantation), pre-operative and post-operative rhythm, inotropic agents used, pre-operative transthoracic echocardiography (TTE) examination, pre- and post-operative 3rd day and 6th month Pro-BNP levels. Further investigations including post-operative 6th month TTE, duration of ECC, aortic cross clamp time, numbers of grafts used, cardiac rhythm and invasive systemic blood pressures during and after levosimendan administration, extubation time, cardiovascular surgical intensive care unit (CVICU) stay, implantation of intra-aortic balloon pump were also realised and analysed.

Sample Collection and NT-proBNP measurements:

Plasma NT-proBNP were studied from peripherol venous blood samples obtained on; (1) the day before surgery, (2) on the 3rd post-operative day and, (3) at the 6th post-operative month. For plasma NT-proBNP measurements blood samples were obtained through an intravenous cannula that was placed 30 minutes before sampling, while the patient resting quietly with semi-recumbent. Samples were collected in chilled Vaccutainers that contained ethylenediaminetetraacetic acid, placed on ice, and centrifuged 20 minutes at -4ºC. Plasma was stored at -80ºC until assay. Creatinine clearance was calculated for each patient.

Plasma NT-proBNP measurements were performed with IMMULITE 1000 TurboNT-proBNP which is a solid phase two site chemiluminescent immunometric assay kit (SIEMENS Healthcare Diagnostic Products Ltd. UK. Catalog#: LSKNT1, manufactured under license from ROCHE Diagnostic GmbH).

Cardiologic Examinations and Two-Dimensional Echocardiography:

All cardiologic examinations were performed by the same cardiologist. Patients underwent TTE using a standard protocol on commercially available systems (Vivid-i GE Vingmed Ultrasound, Horten, Norway). Two-dimensional, M-mode, Doppler and Tissue Doppler Imaging (TDI) echocardiography were performed at rest, with the patient at left lateral decubitis position. All measurements were made according to the American Society of Echocardiography guidelines (13). The left ventricular (LV) and right ventricular (RV) end-diastolic diameters and left ventricular ejection fractions (LVEF) were measured from the apical four-chamber view using the modified Simpson's single plane method (14).

Anestheti Technique:

Patients were premedicated 30 minutes before surgery with 0.05 mg/kg im midazolam (Dormicum; Roche Pharmaceuticals, Nutley, NJ, USA). Following induction of anesthesia (with 2% lidocaine, midazolam 0.05mg/kg, fentanyl citrate (Abbojet; Abbott Laboratories, Abbott Park, III, USA) 25-30 mcg/kg, ketalar (20:1 ratio vs dormicum), etomidate 0.2 mg/kg and pancuronium (Pavulon; Santa Farma, United Arab Emirates) 0.1 mg/kg) intubation was performed. Pulmonary artery catheter (Swan-Ganz Catheter, Edwards, Irvine, Calif, USA) was placed into the right internal jugular vein. Anesthesia was maintained with TIVA (propofol 2% 0.05 mg/kg/min and remifentanyl 25mcg/kg/min) infusion, within each 2 hours, with 2 mg of pancuronium administration.

Surgical Technique:

All operations were performed by the same surgical team. Median sternotomy was performed to all patients. In situ left internal mammary artery (LIMA) was the graft of choice for the revascularization of the left anterior descending artery (LAD) while saphenous vein grafts were used for the remaining coronary vessels. ECC was conducted at 32 ºC via membrane oxygenator (Dideco Compactflo EVO, Dideco, Sorin Group, USA) and a roller pump (Maquet Jostra HL20, Maquet, CA, USA). All coronary distal anastomoses were performed using 7-0 or 8-0 polypropylene sutures with a continuous suturing technique. The proximal anastomoses were also constructed with continuous technique using a side-biting clamp during the rewarming period.

Statistics :

Data was assessed using SPSS v11 (SPSS Inc. Chicago, USA) software package on Windows XP (Microsoft Corp., USA) operating system. Variables, frequency and percentages were expressed in arithmetical means and standard deviation. Compatibility of continuous variables to normal distribution was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Statistical analyses were performed with Paired T Test and Pearson correlation test on variables with normal distribution, while variables without normal distribution were analysed using Wilcoxon and Spearman correlation tests. The

levels of significance are indicated by "p" values. All "p" values equal to or less than 0.05 were considered to indicate statistical significance.

Results

Levosimendan was used in 42 patients (36 male and 6 female) undergoing CABG. Mean age was 61.36±9.1 years (min:39, max:77). Demographic variables are listed in Table 1.

Fourteen patients had previous treatment with percutaneous transluminal coronary angioplasty (PTCA) and stent implantation, and 1 patient had a previous CABG procedure. Six cases were referred to surgery under emergency conditions. In addition to levosimendan infusion, all patients received 5-15 mcg/kg/min dopamine, 39 were additionally administered 0.03-0.2 mcg/kg/min adrenalin and 9 were additionally given 6-20 mcg/kg/min dobutamine perfusion. Per-operative data of the patients are summarised in Table 2.

There were 7 in-hospital deaths (16.6%). Two patients died per-operatively and the remaining died during CVICU follow-up. There were 3 sternal dehiscences with sternal wound infections (7.1%). An intra-aortic balloon pump was implanted in 4 patients (9.5%). Mean extubation time of patients was 18.34±6.2 hours (min/max: 9/34). Mean hospitalisation in the CVICU was 5.45±2.3 days (min/max: 1/15). Post-operative data of the patients are shown in Table 3.

Pre- and post-operative TTE findings of 34 patients, since 8 patients died during either short or long term follow up, are compared in Table 4. Earliest post-operative assessment was performed at the 8th post-operative month whereas the latest was at the 12th month.

Pro-BNP values were measured in pre-operative period, post-operative 3rd day and 6th month (Table 5A, 5B). Accordingly, increase in pro-BNP from pre-operative period to post-operative 3rd day was significant (p 0.047), but the difference between pre-operative and post-operative values was found to be insignificant (p=0.4).

Levosimendan was infused at a rate of 0.1 mcg/kg/min for 24 hours, without per-operative loading dose. At the 23rd hour of perfusion and after 1 hour following discontinuation of perfusion; heart rate and invasive systolic/diastolic blood pressures were recorded (Table 6). Although there were no statistically significant

Table 1: Pre-operative demographic data of the patients. (Pre-op: Preoperative, LVEF: Left ventricular ejection fraction, HT: Hypertension, HL: Hyperlipidemia, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, MI: Myocardial infarction)

Age (years)	61.36±9.1	(min/max: 39/77)
Sex (M/F)	36 / 6	N=42
Preop LVEF (%)	33.9±8.5	(min/max: 20/40)
HT	22	52.38 %
HL	17	40.47 %
DM	24	57.14 %
COPD	9	21.42 %
RECENT MI	32	76.19 %

Table 2: Per-operative data of the patients. (Pre-op: preoperative, PTCA: Percutaneous transluminal coronary angioplasty, CPB: Cardiopulmonary bypass, X Clamp: Aortic cross clamp).

Pre-op PTCA-Stent/Redo Surgery	14/1	35.7%
Emergency cases (n)	6	14.2%
Grafts used (n)	3.950.987	(min/max:2/7)
CPB Time (minute)	181.29102.366	(min/max:57/657)
X Clamp Time (minute)	85.3834.286	(min/max:23/220)
Dopamine (n)	42	100%
Adrenaline (n)	39	93%
Dobutamine (n)	9	21%

Table 3: Post-operative data of the patients. (IABP: Intra-aortic balloon pump, CVICU: Cardiovascular intensive care unit).

Exitus (n)	7	16.6%
Dehiscence (n)	3	0.71%
IABP use (n)	4	9.5%
Extubation time (hr)	18.34±6,2	(min/max: 9/34)
CVICU stay (days)	5.45±2.3	(min/max: 1/15)

Table 4: Pre-operative and post-operative TTE data. LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, RVEDD: Right ventricular end-diastolic diameter.

Parameters	**Pre-op TTE (n:34)**	**Post-op TTE (n:34)**	**p**
LVEF (%)	33.9±8.5 (min/max:20/40)	38.2±6.9 (min/max:25/60)	*0.0001*
Left Atrial Diameter (cm)	4.19±0.54 (min/max:3.2/5.4)	4±0.3 (min/max:3.3/4.9)	*0.007*
LVEDD (cm)	5.7±0.6 (min/max:4.4/7.2)	5.4±0.6 (min/max:4.2/6.9)	*0.001*
RVEDD (cm)	2.3±0.3 (min/max:1.1/3)	2.3±0.2 (min/max:1.8/2.9)	*0.001*

change in heart rate (p=0.13), increase in systolic and diastolic pressures were discovered statistically significant (p<0.0001).

Heart rhythm alterations of the patients in both pre-operative period and following discharge are demonstrated in Table 7. Both atrial fibrillation (AF) and ventricular extrasystoles (VES) were present in 3 of all cases (7.14%). Implantation of permanent pacemaker was required in 1 patient (2.38%). Post-operative rhythm is missing in two patients due to per-operative exitus. Accordingly, no additional rhythm-related problems associated with levosimendan perfusion occurred in the study.

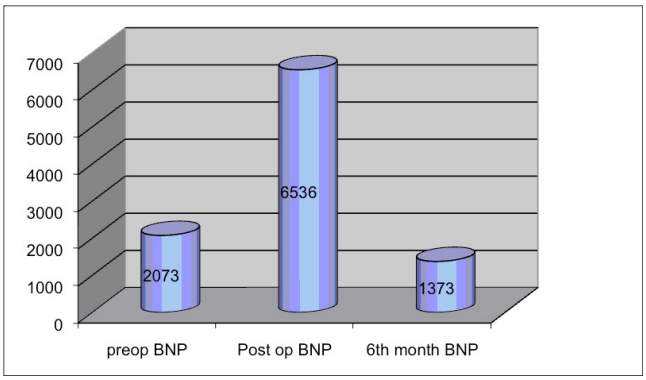
Discussion

It is noticed that levosimendan administration has not been standardised yet. Different teams apply various dose and timing regimens. No real consensus can be established on the loading dose (8-24 mcg/kg/min), maintenance dose (0.05-0.6 mcg/kg/min), timing of the administration (pre-operatively, per-operatively, post-operatively or post-operatively if difficulty is experienced in weaning from the CPB) (15-18). In this study we administered levosimendan pre-operatively, in the beginning of ECC, to patients who had poor LVEF (who we considered at high risk) at a rate of 0.1 mcg/kg/min for 24 hours without a loading dose. Despite the fact that its use is not standardised in most of the reports, they do acknowledge benefits of levosimendan. These reports commonly highlighted similar observations regarding the treatment of levosimendan such as, decrease in myocardial injury, reduction in tracheal intubation time, less requirement for inotropic support, and a shorter length of ICU stay (15,16). Similar results were also reported in our study.

It was pointed out that levosimendan administration may be associated with hypotension especially when used in loading dose. Therefore, it is mandatory to manage the blood pressure and titrate the dose accordingly (19). We did not observe such a complication owing to the fact that, according to our protocol levosimendan was started during the ECC procedure at a low dose, without a loading dose. Moreover, although it was reported that effects of levosimendan on blood pressure and heart rate may last for 3-4 and 7-9 days respectively (20), in our study 14 mmHg mean increase in the systolic and 5 mmHg mean increase in the diastolic blood pressure exactly one hour following discontinuation of levosimendan were recorded. Besides, no increase in the heart rate was observed.

Although it was reported in studies conducted by Raja et al. that heart rhythm disturbances such as ventricular arrhythmias may occur related to levosimendan administration, we did not observe any rhythm disturbances in this study (21). Since effects of levosimendan are dose-dependent, we may predict that afore-

Table 5A, 5B: Diagram (5A) and table (5B) demonstrating levels of pro-BNP values in the pre-operative, post-operative 3rd day and post-operative 6th month.



	Min	Max	Mean
Pre-op BNP (pg/ml)	97	6293	2073±2067.442
Post-op 3rd day BNP (pg/ml)	1481	27627	6536±7622.276
Post-op 6th month BNP (pg/ml)	226	3150	1373±1130.299

Table 6: Heart rate and blood pressure values on the 23rd hour of levosimendan infusion and after 1 hour following discontinuation of infusion. (BP: Blood pressure)

	On the 23rd hour of levosimendan perfusion (n:40)	**One hour after levosimendan cessation (n:40)**	**p**
Heart rate (beat/mn)	90±14 (min/max: 60/130)	88±14 (min/max: 60/140)	0.13
Systolic BP (mmHg)	104±9.6 (min/max: 80/130)	118±12 (min/max: 95/156)	*0.0001*
Diastolic BP (mmHg)	56±5.4 (min/max: 50/70)	61±4.3 (min/max: 45/70)	*0.0001*

Table 7: Pre-operative and post-operative rhythm changes in patients. (Rhythms could not be recorded in two patients due to per-operative exitus. Both AF and VES were present in three of all cases. (NSR: Normal sinus rhythm, AF: Atrial fibrillation, VES: Ventricular extrasystole).

	Pre-op Rhythm (n=42)	**Post-op Rhythm (n=40)**
NSR	35	32
AF	5	5
VES	4	3
Block	1	2
Complete Block	0	1

mentioned arrhythmic events did not occur due to our low dose regimen in the absence of a loading dose (22).

Brain natriuretic peptide (BNP) is a polypeptide neurohormone, which is mainly produced by cardiomyocytes and secreted into the blood where it is cleaved into active BNP and inactive metabolite N-terminal-pro-BNP (NT-pro-BNP) in response to the increased wall stretch (ventricular volume expansion and pressure overload). Thus, pro-BNP is used as an excellent marker in the diagnosis and prognosis of left ventricular dysfunction (23). Pro-BNP values of patients were measured at the pre-operative period and the 3rd post-operative day where it is expected to reach its peak level, and also at the 6th month when it is expected to restore into normal levels. Kyrzopoulos et al. stated that levosimendan reduces BNP values better, compared to the control group (24). In our experience we found a significant pro-BNP increase in the 3rd post-operative day compared to pre-operative values which were also restored to their normal range at the 6th post-operative month.

Following pre-operative TTE, the subsequent TTE control was scheduled for the 8th post-operative month and the final control examination was programmed for the 12th month. Tasouli et al. also reported significant increase in LVEF which is about 12% and significant decrease in left atrial, left ventricular diastolic and right ventricular diameters following levosimendan administration (17). Our results are similar with these reports. All TTE examination findings were found to be statistically significant in our study.

Another important point about starting a new inotropic agent is the expectation regarding reduction of other conventional inotropic drugs dosages. This expectation is not yet realistic. In a study published by Levin and De Hert, authors stated that the additional inotropic agent dosage is diminished in patients receiving levosimendan (25, 26). In our study, in addition to levosimendan, 3 patients received only dopamine, 30 patients dopamine and adrenaline and 9 patients received dobutamine in addition to dopamine and adrenalin.

In studies conducted by Harjola et al. it was defined that patients receiving levosimendan could be successfully weaned from ECC (27). Two of our cases died in the per-operative period despite all interventional efforts. Four other cases could be weaned from the ECC with IABP application.

In a study of Gurbuz et al., authors emphasised the importance of the timing of the drug administration (18). Tasouli et al. also underline the initial topic and concluded that while early administration of levosimendan perfusion leads to better outcomes, pre-operative or per-operative administration generated similar effects (17). In our present study, we administered levosimendan per-operatively to all patients in correlation with the former reports. Raja et al. also reported that levosimendan may be used as rescue therapy in patients experiencing difficulty in weaning from the CPB (21). Cobanoglu et al. reported that levosimendan would aid weaning from ECC following the coronary bypass surgery (28).

However, our limited case number necessitates a more comprehensive study to confirm these findings and to assess the comparative values of patients who are in the high-risk group. Further researches should be undertaken to compare all surgical options and clearly evaluate results of levosimendan administration in long term period.

Limitations:

This study clearly demonstrates that levosimendan could be used safely in high-risk patients. Methodological limitation of the study is the lack of a control group as, following it's presence in the clinical use since 2006, levosimendan is used in every patient as an additional inotropic drug when myocardial support becomes essential. However a study where we make comparisons by one-on-one matching our patient group with patients treated with different modalities in the 'before levosimendan era' is currently ongoing.

Acknowledgement:

The authors express their gratitude to Prof. Nuran INCE, MD, (Department of Public Health, Istanbul Faculty of Medicine, Istanbul University, Istanbul) for the analysis of the statistics and her help in the evaluation of the data.

Declaration of conflict of interest:

This study was not supported by any individual, institute and organisation other than own sources of our clinic. None of authors had financial or immaterial relation with any company, institute or organisation.

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