J Anesth (2014) 28:347–353
DOI 10.1007/s00540-013-1741-2

ORIGINAL ARTICLE

Taurine attenuates lung ischemia–reperfusion injury after lung transplantation in rats

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Received: 3 April 2013 / Accepted: 19 October 2013 / Published online: 6 November 2013
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Abstract
Purpose Taurine, the major intracellular free amino acid found in high concentrations in mammalian cells, is known to be an endogenous antioxidant and a membrane-stabilizing agent. It was hypothesized that taurine may be effective in reducing ischemia–reperfusion injury after lung transplantation and an experimental study was conducted in a rat model.
Methods The number of Sprague–Dawley rats used in the study was 35. Animals were randomized into five groups of 7 rats each, including control, donor I, donor II, ischemia–reperfusion injury, and treatment groups. All animals were exposed to the same experimental conditions in the preoperative period. Rats were fixed in a supine position after the induction. After the rats were shaved, a left pneumonectomy was performed following sternotomy in control, donor I, and donor II groups. The harvested grafts in donor I and donor II groups were transplanted to the rats of the ischemia–reperfusion group and treatment group, respectively. However, taurine was administered intraperitoneally for 3 days before the harvesting procedure in donor II. All harvested lungs were kept in a Euro-Collins solution at +4 °C for 24 h in a half-inflated manner. After harvesting and transplantation, lungs were sampled for histopathological and biochemical analysis.
Results Malondialdehyde and superoxide dismutase, glutathione peroxidase, and catalase levels were lower in the treatment group than the other groups ($p < 0.05$). Histopathological findings were better in treatment group than the ischemia–reperfusion group ($p < 0.05$).
Conclusion It was demonstrated that donor treatment with taurine resulted in preservation of transplanted lung tissue in respect to histopathological and biochemical findings.

Keywords Lung transplantation · Rat model · Ischemia–reperfusion injury · Taurine

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Introduction

Lung transplantation has become an effective therapeutic option in the treatment of patients with end-stage pulmonary diseases. However, acute graft dysfunction continues to be a serious obstacle to successful lung transplantation. It is mainly caused by pulmonary ischemia–reperfusion injury (IR/I) and leads to significant postoperative morbidity and mortality [1].

Pulmonary ischemia–reperfusion injury is characterized by increased pulmonary vascular resistance, poor oxygenation, worsened compliance, and increased capillary permeability, leading to edema formation. The ischemic insult to the lung results in cytokine production and increased expression of adhesion molecules by hypoxic lung cells. The injury cascade is mediated mostly by neutrophil-endothelial adherence and subsequent neutrophil-mediated organ injury. Activated neutrophils secrete reactive oxygen species (ROS) and proteolytic enzymes that result in structural and functional injury to the lung parenchyma [2].

Several studies have shown that agents such as prostaglandins; the oxygen free radical scavengers superoxide dismutase, catalase, glutathione, allopurinol, dimethyl thiourea, lazaroids, and trimetazidine; aprotinin; platelet factor antagonists; and angiotensin-converting enzyme inhibitor, captopril, melatonin and others to be effective in protecting lungs against IR/I [2–8].

Taurine (2-aminoethanesulfonic acid), the major intracellular free amino acid found in high concentration in mammalian cells, is known to be an endogenous antioxidant and a membrane-stabilizing agent. Taurine is demonstrated to reduce IR/I of livers after transplantation [9], protects hearts from myocardial infarction in rats [10], and may decrease myocardial damage during the cold ischemic period following global myocardial ischemia in rats [11]. Taurine administration has useful effects against lung injury after re-expansion [12]. We hypothesized that taurine may also be effective in reducing IR/I after lung transplantation and conducted this experimental study in a rat model.

Materials and methods

Animals

All procedures performed on animals were in accordance with the European Union Directive 609/86 for care and use of laboratory animals. The study was approved by the experimental ethics committee. Male Sprague–Dawley rats (weight 250–350 g) were obtained from the Health Sciences Institute. They were maintained in a temperature-controlled animal room with a 12-h light–dark cycle. Before the experiment, all animals were fed with rat chow and water ad libitum. In a pre-operative setting, each animal was placed in a closed dome, and then isoflurane was administered via inhalation. After sedation, animals underwent mask ventilation. The tail artery was cannulated with a tube (PE-50) for monitoring of arterial pressure and the vein was cannulated for intravenous saline or drug administration. Throughout the experiment, the rats' body temperature was maintained at 36.5–37.5 °C by a heating pad, and saline solution was infused using a perfusor at a constant rate of 10 ml/kg/h. Electrocardiographic leads attached to subcutaneous electrodes were used to monitor limb lead II. Following mask ventilation, tracheostomy and tracheal intubation was performed with a 16-gauge catheter and rats were mechanically ventilated with 100 % oxygen. The ventilation rate was 80 breaths/min, and the tidal volume was 15 ml/kg. The inspiratory/expiratory ratio was 1:1. The rats were anesthetized with an intraperitoneal injection of 75 mg/kg ketamine following isoflurane (1–3 %) administration. Electrocardiogram (ECG), systolic, diastolic and mean arterial pressure (MAP), and heart rate (HR) were continuously monitored. Before the sternotomy, each rat was administered 15 U unfractioned heparin intravenously.

The number of Sprague–Dawley rats used in the study was 35. Animals were randomized into five groups of 7 rats each. The groups are listed in Table 1.

The IR/I model used in the study was easy to apply for experimental lung transplantation in laboratory animals, defined previously by Yücel et al. [13]. In this model, while harvesting the donor lung, the pulmonary artery and vein, and main bronchus were dissected distally to ease connection between donor and recipient vasculature during implantation. Then the bronchus of the transplanted lung was ventilated using a different endotracheal tube.

Control group (CG)

All animals were exposed to the same experimental conditions during the preoperative period. Rats were fixed in a supine position after induction. After the rats were shaved, a left pneumonectomy was performed following sternotomy. The left lung was sampled for histopathological examination and biochemical analysis. The rats of the

Table 1 Animal groups

Group	Number of rats	Donor (±)	Recipient (±)	Taurine administration (±)
Control group (CG)	7	−	−	−
Donor group (DG) 1	7	+	−	−
I/R group (IRG)	7	−	+	−
Donor group (DG) 2	7	+	−	+
Treatment group (TG)	7	−	+	−

control group were sacrificed by infusing a lethal dose of anesthetics after sampling.

Donor group I (DG-I)

The left lungs in donor group I were harvested as allografts for transplantation and sampled for histopathological examination and biochemical analysis. While harvesting, left pulmonary hila were dissected proximally to provide long-length vasculature and bronchus to ease the transplantation procedures. Following dissections, the left main pulmonary artery and veins were cannulated, then the left main bronchus was intubated with an appropriate sized tube for mechanical ventilation. Then rats were sacrificed by infusing a lethal dose of anesthetics after harvesting the allografts.

The catheter placed into the left main pulmonary bronchus was combined with a three-line valve system. The first line was connected to the bronchus, the second line was connected to the pressure system and the last one was connected to a ventilator for manual ventilation.

The graft was irrigated with an infusion of Euro-Collins solution at a pressure of 1.5 cm H_2O by way of a catheter inserted in the left main pulmonary artery. During irrigation, the graft lung was ventilated manually at a rate of 80 breaths/min. The maximum positive end expiratory pressure (PEEP) was 1.5 cm H_2O. The graft was kept in the Euro-Collins solution at +4 °C for 24 h in a half-inflated manner. Finally, grafts were transplanted into the rats in the IRG group at the end of a 24-h time period. Reperfusion and reventilation was re-established after this period of time.

Donor group II (DG-II)

The same protocol mentioned above was applied to the rats in donor group II, but unlike DG-I, Taurine (100 mg) (Nutra Manufacturing Inc., Greenville, SC, USA) was administered intraperitoneally for 3 days before the harvesting procedure. After harvesting, grafts were sampled for histopathological examination and biochemical analysis, and afterwards transplanted into rats in the treatment group.

I/R group (IRG)

Left pneumonectomy was performed in a similar fashion as described in DG-I, however, in IRG, left pulmonary hila were dissected distally to provide long-length graft vasculature and bronchus to ease the transplantation procedures. After dissection and securing recipient vasculature and main bronchus, left lungs were removed. Subsequently, previously harvested lungs, kept in the Euro-Collins solution at +4 °C for 24 h in a half-inflated manner in DG-I, were transplanted into the rats. After transplantation, rats were ventilated manually at a PEEP of 1.5 cm H_2O with a ventilation rate of 80 breaths/min and tidal volume of 1.2 ml. Allografts were ventilated in the same manner, but by a different catheter. Allografts were sampled for histopathological and biochemical analysis after 2 h of the reperfusion and reventilation processes.

Treatment group (TG)

Rats in the treatment group had the same protocol as described for IRG. The only difference between IRG and TG was the source of harvested grafts. Grafts transplanted to rats in group IRG were provided from the rats in DG-I, and grafts transplanted to rats in TG were provided from the rats in DG-II. The sampling for histopathological examination and biochemical analysis were performed after 2 h of reperfusion and reventilation processes.

Histopathological investigation

After routine procedures, lung samples were embedded in paraffin blocks. A pathologist evaluated the histopathological findings blindly. Peribronchial lymphocytic infiltration, inflammatory infiltration in perivascular and/or parenchyma, perivascular edema, alveolar edema and congestion were investigated in all slides. The intensity of findings was graded using a 4-stage grading scale (negative, 0; mild, 1; moderate, 2; strong, 3).

Laboratory methods

All tissues were homogenized with ice-cold KCl (1.15 %) using a glass homogenizer. The homogenates were then centrifuged at 4,400 *g* for 10 min at 4 °C to remove the cell debris and the supernatant obtained was used for the determination of malondialdehyde (MDA) and antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT).

MDA, CuZn-SOD, GPx and CAT activities were measured on a UV–VIS recording spectrophotometer (UV-2100S, Shimadzu Co., Kyoto, Japan). The levels of tissue malondialdehyde (MDA) were measured with the thiobarbituric acid reactive substances by the method as described by Al-Fawaeir et al. [14]. Following occurrence of the reaction between MDA and thiobarbituric acid, the reaction product was followed spectrophotometrically at 532 nm, using tetrametoxypropane as a standard. The MDA content was expressed as mmol/g protein.

CuZn-SOD activity was measured as previously described by Eken et al. [15]. Briefly, 50 µl of the supernatant was mixed with 850 µl of the substrate solution containing 0.05 mmol/l xanthine sodium and 0.025 mmol/l 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT) in a buffer solution containing 50 mmol/l CAPS (3-(cyclohexylaminol)-

1-propanesulfonic acid) and 0.094 mmol/l EDTA (pH 10.2). To this mixture,100 µl xanthine oxidase (80 U/l) was added and the increase of absorbance was followed at 505 nm for 3 min. CuZn-SOD activity is expressed in U/g.

GPx activity was measured as previously described by Eken et al. [15]. Briefly, a reaction mixture containing 1 mmol/l Na_2EDTA, 2 mmol/l reduced glutathione, 0.2 mmol/l NADPH, 4 mmol/l sodium azide and 1,000 U glutathione reductase in 50 mmol/l TRIS buffer (pH 7.6) was prepared. A mixture was made of 50 µl of the supernatant and 950 µl of the reaction mixture, and incubated for 5 min at 37 °C. The reaction was initiated by adding 8.8 mmol/l hydrogen peroxide and the decrease of absorbance recorded at 340 nm for 3 min. GPx activity is expressed in U/g.

CAT activity was measured in the supernatant at 25 °C using the method of Aebi et al. [16]. The decomposition rate of the substrate H_2O_2 was monitored in a spectrophotometric analysis at 240 nm for 30 s. The activity is expressed as MU/g. One unit (U) is equal to 1 µmol of H_2O_2 decomposed/min.

Lipid peroxidation was estimated by measurement of thiobarbituric acid reactive substances (TBARS) in the supernatant by the method previously described by Eken et al. [15]. After the reaction of MDA with thiobarbituric acid, the reaction product was followed in a spectrophotometric analysis at 532 nm, using tetrametoxypropane as a standard. The results are expressed as nmol/g.

Statistical analysis

Statistical analyses were performed using SPSS software for Windows version 17.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA). Continuous variables were expressed as 'mean values ± standard deviation (SD)'. A Kruskal–Wallis test was used to compare the enzyme levels between the groups. The Bonferroni corrected Mann–Whitney *U* test was used to document the group which demonstrated differences. A *p* value less than 0.05 was considered statistically significant for all comparisons.

Results

Biochemical results

In terms of biochemical parameters, including MDA, SOD, GPx, and CAT, a statistically significant difference was determined among all groups ($p < 0.001$, Kruskal–Wallis test, Table 2). With binary comparisons according to the Bonferroni corrected Mann–Whitney *U* test, statistically significant differences were observed between control and I/R groups, between control and treatment groups, and between I/R and treatment groups in terms of MDA, SOD, GPx, and CAT. Enzymatic results and statistical analysis of groups are summarized in Table 2.

Histopathological results

There were similar, but statistically significant differences in histopathological findings among groups ($p < 0.001$, Kruskal–Wallis test). However, when the intensity of histopathological changes were compared, statistically significant differences were observed in binary comparisons of groups. There were statistically significant differences between the control and I/R group, between I/R and treatment, and between donor II (drug) and treatment groups ($p < 0.001$, Mann–Whitney *U* test) for all histopathological findings, including peribronchial lymphocytic infiltration, intra-alveolar macrophages, perivascular edema, alveolar edema and congestion ($p < 0.05$), but a statistically significant difference was not observed between control and donor I, nor between control and donor II ($p > 0.05$). The intensity of these histopathological findings in the treatment group were lesser than in the ischemic ones. Histopathological results are summarized in

Table 2 Enzymatic results and statistical analysis of groups

	Mean ± SD					
	Control	Donor I	I/R	Donor II (drug)	Treatment	*p* value*
MDA (mmol/g protein)	9.16 ± 0.08	9.19 ± 0.12	17.02 ± 0.08	9.16 ± 0.70	12.39 ± 0.15	<0.001
SOD (U/g protein)	701.00 ± 23.40	702.57 ± 25.65	551.71 ± 52.98	730.87 ± 21.81	1016.58 ± 97.02	<0.001
GPx (U/g protein)	14.64 ± 0.72	14. 60 ± 1.12	16.51 ± 0.79	14.72 ± 1.79	18.89 ± 2.68	0.002
CAT (MU/g)	4.49 ± 0.22	4.42 ± 0.30	3.10 ± 0.17	51.17 ± 0.60	6.26 ± 0.58	<0.001

Results of biochemical tests for each group

MDA malondialdehyde, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *CAT* catalase

* Kruskal–Wallis test

Table 3 Histopathological findings and statistical analysis of groups: histopathological results

	Mean ± SD					
	Control	Donor I	I/R	Donor II (drug)	Treatment	*p* value*
PBLI	0.14 ± 0.37	0.14 ± 0.37	3.29 ± 0.75	0.14 ± 0.37	1.86 ± 0.69	<0.001
PMI	0.14 ± 0.37	0.29 ± 0.48	1.43 ± 0.53	0.14 ± 0.37	1.14 ± 0.37	<0.001
PVPLI	0.43 ± 0.53	0.29 ± 0.48	2.71 ± 0.75	0.14 ± 0.37	1.57 ± 0.53	<0.001
PLI	0.14 ± 0.37	0.29 ± 0.48	3.14 ± 0.9	0.14 ± 0.37	2.43 ± 0.97	<0.001
PVLI	0.14 ± 0.37	0.29 ± 0.48	3.57 ± 0.53	0.14 ± 0.37	2.29 ± 0.48	<0.001
PPLI	0.14 ± 0.37	0.29 ± 0.48	3.57 ± 0.53	0.14 ± 0.37	2.29 ± 0.75	<0.001
PVE	0.43 ± 0.53	0.43 ± 0.53	3.71 ± 0.48	0.43 ± 0.53	2.86 ± 0.69	<0.001
AE	0.43 ± 0.53	0.29 ± 0.48	4. 00 ± 0	0.29 ± 0.48	3.14 ± 0.69	<0.001
C	0.71 ± 0.48	0.71 ± 0.48	4. 00 ± 0	0.71 ± 0.48	3.00 ± 0.81	<0.001

The intensity of findings was graded using a 4-stage grading scale (negative, 0; mild, 1; moderate, 2; strong, 3), and represented as mean ± SD

PBLI peribronchial lymphocytic infiltration, *PMI* parenchymal macrophages infiltration, *PVPLI* perivascular PMN leukocyte infiltration, *PLI* parenchymal lymphocytic infiltration, *PVLI* perivascular lymphocytic infiltration, *PPLI* parenchymal PMN leukocyte infiltration, *PVE* perivascular edema, *AE* alveolar edema, *C* congestion

* Kruskal–Wallis test

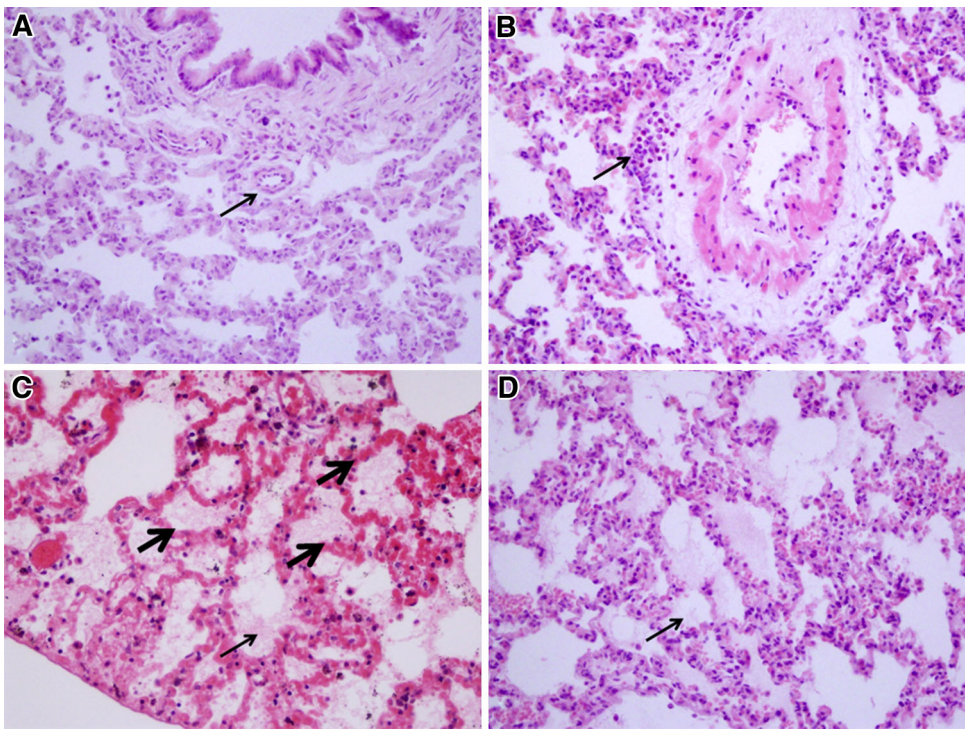

Fig. 1 **a** Normal peribronchial lung parenchyma and vascular structure (*arrow*) (HE×100) (control group). **b** Perivascular edema and PMN leukocyte infiltration (*arrow*) in I/R group (HE×200). **c** Congestion (*thick arrows*) and alveolar edema (*thin arrow*) in I/R group. **d** The intensity of congestion and alveolar edema (*arrow*) in the treatment group was less than in the ischemic ones

Table 3. Histopathological differences among groups are demonstrated in Fig. 1.

Discussion

In the present study, we evaluated the protective effects of taurine in a rat single-lung transplantation model of ischemia–reperfusion injury. The aim of the study was to determine the protective effect of donor treatment with taurine on post-transplant lung ischemia–reperfusion injury. We compared this group with a control group without transplantation, and an ischemic control group subjected to the same prolonged cold ischemic storage, followed by transplantation without any treatment. We found that donor treatment with taurine resulted in significant improvement of graft histopathological and biochemical preservation of lung tissue MDA, SOD, GPx, and CAT levels.

Ischemia–reperfusion-induced pulmonary dysfunction is a significant clinical problem in lung transplantation. Potentially life threatening graft dysfunction early after

lung transplantation can occur in up to 20 % of patients [17]. I/R includes two phases: (1) ischemia, which is related to lack of oxygen, cell damage, and activation of cytotoxic enzymes, and (2) reperfusion, which is associated with formation of reactive oxygen intermediates, platelet and neutrophil activation, endothelial cell injury, increased vascular permeability, cytokine activity and complement activation. Throughout the ischemic phase of I/RI, when oxygen, ATP and other high-energy phosphates are depleted, conversion from aerobic to anaerobic cellular metabolism causes formation of cytotoxic metabolites. With re-establishment of perfusion, the injury elicited by reperfusion can be more severe than that caused by ischemia. Pulmonary I/RI also results from the combined effects of ischemia and reperfusion and involves changes in cellular energy metabolism as well as production of ROS. Amplification of the inflammatory response, and adherence of activated platelets and neutrophils to damaged endothelial cells may cause pulmonary vascular dysfunction and obstruction [18].

Taurine (2-aminoethanesulfonic acid), the major intracellular free amino acid found in high concentrations in mammalian cells, is known to be an endogenous antioxidant and a membrane-stabilizing agent. Up to now, many studies have documented the protective effects of taurine against an array of damaging stimuli, including ischemia/reperfusion (I/R), hyperglycemia, ROS, heat shock, toxic xenobiotics, cellular excitotoxicity, and osmotic derangements. Most recently, taurine has been clearly demonstrated to improve graft survival after cold ischemia and subsequent liver transplantation [19], and to protect livers from warm I/R [9] and hearts from myocardial infarction in rats [10]. Guan et al. [20] demonstrated donor preconditioning with taurine protects kidney grafts from injury, improves graft function, and increases the regenerative potential via mechanisms including antioxidation. Yücel et al. [12] showed that taurine administration has useful effects against the lung injury after re-expansion. They explained that the mechanisms of the protective effects of taurine may be related to the decrease of MDA level and the increase of SOD and GPx activity. However, to date, limited information is available regarding the relationship between taurine and lung I/R.

In our study an easily applicable model of ischemia and reperfusion on lung transplantation, which is described by Yücel et al. [13], is used. In contrast to other experimental techniques requiring microsurgical interventions, it is simple and cheap.

A reduced antioxidative capacity, which is known to occur after I/R, is associated with lipid peroxidation and injury to the graft. Following administration of taurine, we observed an enhanced antioxidative capacity, which was demonstrated by increased expression of SOD accompanied by less cellular injury. Changes in CAT, GPx and MDA levels in our study show that taurine is effective in the prevention of IR/I in the rat lung transplantation model.

I/R injury is associated with severe structural and functional pulmonary alterations, e.g. intra-alveolar and interstitial edema or loss of blood–air barrier integrity. The present study was performed on a reliable isolated lung model that allows us to study the consequences of the sequence of transplantation related events including lung preservation, ischemic storage and subsequent reperfusion. Pulmonary edema is a hallmark of acute lung injury (ALI) and shows a sequential development within the different compartments of the lung [21]. In the present study congestion, edema and perivascular polymorphonuclear leukocyte (PMNL) infiltration were observed significantly less in the taurine group. This shows that taurine is effective in the management of IR/I associated ALI.

The present study has several limitations. First, the sample size is small; therefore, conclusions that may be drawn from this study must be treated cautiously. Second, the data presented concentrated on biochemical and histopathological findings: analysing the physiological functions and related data would have provided valuable contributions to the study. Due to technical insufficiency, physiological functions and related data could not be investigated in the treatment and I/R groups. Finally, the most important limitation of this study is that the present data can not be applied to clinical transplantation from a brain-dead donor, because the transplanted lung has not been exposed to the catecholamine storm which follows brain death. However, it may help to initiate more new experimental studies.

In conclusion, in this experimental model, donor treatment with taurine, an amino acid found in mammalian cells, protected the lungs against post-transplantation ischemia–reperfusion injury. Further studies are warranted to assess the impact of taurine in post-transplantation lung ischemia–reperfusion injury.

Acknowledgments Leyla Guler, Murat Tavlasoglu, Orhan Yücel, Adem Güler, and Mehmet Ali Sahin contributed to the pre-operative and operative planning of the groups, and performed the surgical procedures. Mustafa Kurkluoglu, Yusuf Sirin, Ayse Eken, Mehmet Gamsizkan, Mehmet Dakak, Sedat Gurkok, and Onur Genc recorded and analyzed follow-up data. All authors read and approved the final version of manuscript.

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