J Bras Pneumol. 2021;47(5):e20200435
https://dx.doi.org/10.36416/1806-3756/e20200435

ORIGINAL ARTICLE

Chronic thromboembolic pulmonary hypertension: the impact of advances in perioperative techniques in patient outcomes*

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Submitted: 20 February 2020.
Accepted: 27 May 2021.

Study carried out in the Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), Brasil.

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ABSTRACT

Objectives: Pulmonary endarterectomy (PEA) is the gold standard treatment for chronic thromboembolic pulmonary hypertension (CTEPH). This study aimed at reporting outcomes of CTEPH patients undergoing PEA within 10 years, focusing on advances in anesthetic and surgical techniques. **Methods:** We evaluated 102 patients who underwent PEA between January 2007 and May 2016 at the Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo. Changes in techniques included longer cardiopulmonary bypass, heating, and cooling times and mean time of deep hypothermic circulatory arrest and shortened reperfusion time. Patients were stratified according to temporal changes in anesthetic and surgical techniques: group 1 (January 2007–December 2012), group 2 (January 2013–March 2015), and group 3 (April 2015–May 2016). Clinical outcomes were any occurrence of complications during hospitalization. **Results:** Groups 1, 2, and 3 included 38, 35, and 29 patients, respectively. Overall, 62.8% were women (mean age, 49.1 years), and 65.7% were in New York Heart Association functional class III–IV. Postoperative complications were less frequent in group 3 than in groups 1 and 2: surgical complications (10.3% vs. 34.2% vs. 31.4%, p=0.035), bleeding (10.3% vs. 31.5% vs. 25.7%, p=0.047), and stroke (0 vs. 13.2% vs. 0, p=0.01). Between 3 and 6 months post-discharge, 85% were in NYHA class I–II. **Conclusion:** Improvements in anesthetic and surgical procedures were associated with better outcomes in CTEPH patients undergoing PEA during the 10-year period.

Keywords: Pulmonary embolism; Pulmonary hypertension; Endarterectomy; Hospital mortality; Survival analysis; Postoperative complications.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a severe pulmonary vascular disease with high rates of morbidity and mortality.(1-3) CTEPH was recently recognized as a clinical condition, and its incidence following pulmonary embolism ranges between 0.6% and 3%.(4) Thus, pulmonary arteries are exposed to high pressures over a significant period of time, which influences the development of microvascular disease or secondary vascular arteriopathy.(5,6) The prognosis of this condition depends on the degree of associated right ventricular dysfunction and underlying pulmonary hypertension (PH). The 5-year survival rate of CTEPH patients without treatment is 30%, while the mean pulmonary artery pressure (mPAP) is between 40 and 50 mmHg. This rate is even lower, at approximately 10% when mPAP is above 50 mmHg, which highlights the severity of this disease and the need for effective therapies.(7,8)

Pulmonary endarterectomy (PEA) is the gold standard treatment for CTEPH.(5,9-12) PEA surgically removes the obstructing thromboembolic material, resulting in significant improvements in right ventricular hemodynamics and function. In the past few years, adequate patient selection, advanced anesthetic, and surgical techniques and postoperative care have been associated with better outcomes in CTEPH patients.(5-8,11-13) Considering the evident learning curve for the operation and important changes in operative techniques over the years, the mortality rates have decreased from approximately 20% to 4% in reference centers for PEA.(5,6,9-15)

This study aimed at reporting the 10-year experience undergoing PEA in CTEPH patients referred to at a single university hospital in Brazil, emphasizing the influence of advances in surgical, perioperative, and postoperative outcomes, including survival rate within 2 years of follow-up.

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Financial support: None.

METHODS

Study design and participants

This was a retrospective study of CTEPH patients who underwent PEA between January 2007 and May 2016 at the Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (InCor-HCFMUSP), a referral center for PEA. The protocol was submitted and approved by the Scientific Committee (Process No. 495631) of InCor-HCFMUSP. This study followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology initiative.[16]

The patient's selection followed predefined criteria for inclusion in this analysis: i) complete information in the electronic medical records, ii) both sexes and no age restriction, iii) CTEPH diagnosis, and iv) subjected to cardiopulmonary bypass (CPB) and in deep hypothermic circulatory arrest (DHCA) during surgical management. Patients were excluded if CTEPH was not confirmed during a surgical procedure.

Two improvements were made in the surgical techniques and were implemented over 10 years (Figure 1). The first was implemented in January 2013 and consisted of changes in the management of CPB and in the DHCA. The second was implemented in April 2015 and consisted of additional changes in the management of CPB and modifications in surgical and anesthetic techniques (Table 1). In this study, patients were stratified into three groups according to the period of time PEA was performed. Group 1 covers the period from January 2007 to December 2012 and includes 38 patients. Group 2 included 35 patients who underwent PEA between January 2013 and March 2015 after the first modifications in the surgical techniques were implemented. Group 3 included 29 patients who underwent PEA between April 2015 and May 2016 after the second modifications in the surgical techniques were implemented.

There was no calculation of the sample size, considering that all patients were included in the studied period.

Data collection

Data collection was performed using a database created in the Research Electronic Data Capture system. Regarding the preoperative phase, we collected clinical characteristics sucha as laboratory and imaging data, comorbidities, vascular staging, and hemodynamic parameters. In terms of the intraoperative phase, we collected CPB, DHCA, cooling and warming methods, reperfusion, and cardiac arrest time.

Clinical outcomes

Immediate outcomes after surgery, including mortality, were analyzed as 2-year survival rate and functional evaluation. Postoperative outcomes were defined as occurrence of complications[17-27] during the hospital stay.

Detailed description of the clinical outcomes is provided on the supplementary material.

Surgical techniques performed after April 2015 (group 3)

Surgical access was performed by median sternotomy to allow bilateral endarterectomy. CPB was installed after cannulation of the ascending aorta and superior and inferior venae cavae and progressive cooling up to 15°C with neuroprotection. Subsequently, a right pulmonary arteriotomy was performed to initiate thrombus dissection. Circulatory arrest was carried out in period limited to 20-min at a time, with reperfusion at 10-min interval.

Modifications to identify the adequate endarterectomy plane allowed surgeons to perform the operation on patients with thromboembolic disease in the distal segmental and subsegmental branches. After the endarterectomy on both sides, circulation with rewarming was started. During this maneuver, a right and left arteriorrhaphy was performed on the pulmonary arteries, followed by the resumption of the heartbeat. When the body temperature reached 36°C, mechanical ventilation and preparation for CPB disconnection were initiated. After CPB removal, hemostasis, pericardial drainage, and thoracotomy synthesis were performed. Once stabilized, the patient was transported to the ICU.

Anesthetic techniques performed after April 2015 (group 3)

During anesthesia induction, hypotension was prevented by using agents that were not associated with hemodynamic instability. Ketamine, fentanyl, and pancuronium were successfully used. Nitric oxide was started through mechanical ventilation at 10 p.p.m. Phenylephrine was preferentially prescribed as a vasopressor in these patients because of its effects

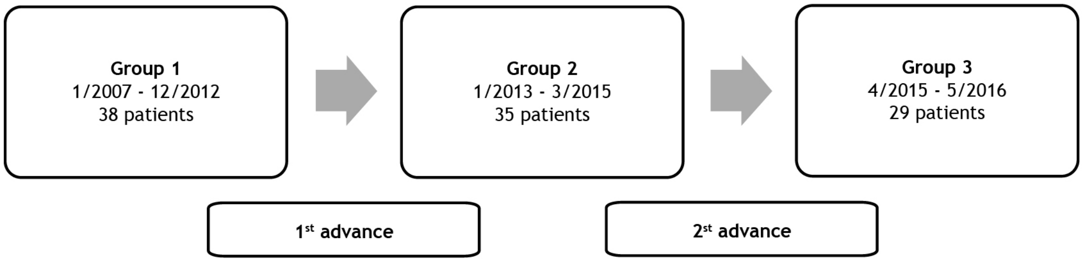

Figure 1. Study population stratified into groups according to time and advances in anesthetic and surgical techniques.

Table 1. Description of advances implemented during the study period.

Standardization of	1st improvement (January 2013)	2nd improvement (April 2015)
Cardiopulmonary bypass	• Cooling duration at least 70 min (up to 15°C) • Rewarm duration at least 90 min (up to 36°C)	• Reduction by half of the total volume of the dilutional prime • Invasive blood pressure monitoring in the radial artery • Temperature control with tympanic thermometer • Brain monitoring with BIS • Cooling jacket of the head after anesthetic induction
Deep hypothermic circulatory arrest	• Each period to up to 20 min • Reperfusion of 10 min between each DHCA	• None
Anesthetic procedure	• None	• Standardization of drugs in anesthetic induction • Hemodynamic control of PH with dopamine and phenylephrine • Femoral artery catheterization • Zero fluid balance (avoiding positive balance) • Use of transesophageal echocardiography • Use of Cell Saver® • Decrease in allogeneic transfusion
Surgical procedure	• None	• Cross-cannulation of the vena cava for the installation of CPB • Installation of a cannula for drainage of cardiac cavities • Use of thinner polypropylene yarns (6.0 and 7.0) for arteriorrhaphy • Use of biological glue after arteriorrhaphy

CPB: cardiopulmonary bypass; BIS: bispectral index; PH: pulmonary hypertension.

on right ventricular performance, maintaining CO, mean arterial pressure, and coronary artery perfusion.

During surgery, overhydration was avoided, using dynamic assessment of fluid status through the analysis of pressure pulse variation, echocardiography, and CO. We used Cell Saver, intravenous antifibrinolytic (aminocaproic acid during surgery), and goal-directed therapies such as prothrombin complex, fibrinogen concentrate, and platelet transfusion pending the diagnosis of the cause of bleeding, and red blood cell transfusion was rarely needed, but in cases with hematocrit <22% during CPB with signs of tissue hypoxia.

Detailed description of the anesthetic techniques performed is provided on the supplementary material.

Statistical analysis

Descriptive analysis of categorical data was expressed using absolute and relative frequencies to assess whether the groups were homogeneous. Differences between groups were evaluated using the chi-square test (Mantel-Haenszel). Analysis of variance or Kruskal-Wallis test was applied to analyze group differences. Continuous data were expressed as means and standard deviations.

Postoperative outcomes (surgical complications, infectious complications, and in-hospital mortality) were analyzed using univariate and multivariate logistic regression models. In this study, the parameters evaluated in the univariate model are presented in the supplementary materials.

After the univariate analysis, variables with $p<0.10$ were included in the multivariate logistic regression model (Tables 1S, 2S in the online-only data supplement). In the multivariate analysis, a value of $p<0.05$ was considered significant, and the odds ratio (OR) and 95% confidence interval (IC) were calculated. For the evaluation of in-hospital mortality, a Pearson correlation analysis was performed using the mPAP, pulmonary arterial systolic pressure (PASP), pulmonary vascular resistance (PVR), and CO. As PVR showed correlation ($p<0.010$) with mPAP, PASP, and CO, it was used in the multivariate model.

Survival analysis was calculated using the nonparametric Kaplan-Meier method, and the survival curves of the three groups were compared using the log-rank test, which was considered significant if $p<0.05$. Data were analyzed using SPSS for Windows version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Participant characteristics

A total of 110 patients underwent PEA during this period. We excluded eight patients: five were not confirmed as having CTEPH during surgery and three underwent a different surgical procedure. Therefore, we included a total of 102 patients in this study (Figure 1S in the online-only data supplement).

Of the 102 patients, 62.8% were female, and the mean age was 49.1 ± 14.8 years (Table 1S). Of all patients who presented with dyspnea, 57.8% showed edema in the lower limbs, 33.3% had chest pain, 23.5% had syncope, and 7.8% had fatigue. Approximately 66% of patients were in New York Heart Association (NYHA) functional class III–IV. Previous single or recurrent pulmonary embolism was confirmed in more than 80% of the patients in each group, and a history of DVT was documented in more than 40% of patients. Thrombophilic disorder was diagnosed in 45 cases (44.1%).

Right ventricular catheterization indicated significant PH with elevated mPAP (mean, 53.2 mmHg and 53.2 ± 13.1 mmHg, respectively) and PVR (869.5 ± 380.2 dyn.s.cm^{-5}). No differences in clinical characteristics and hemodynamic parameters were observed among the three groups.

Surgery

Groups 2 and 3 had longer CPB time and longer cooling and warming time than group 1 (Table 2S). In addition, groups 2 and 3 had longer DHCA time and a lower number of cardiac arrests than group 1. Information on the surgical classification of pulmonary vascular impairment (I to IV) was not available.

Postoperative outcomes

Surgical complications were less frequent in group 3 (10.3%) than in groups 1 and 2 (34.2% and 31.4%, respectively, p=0.035) (Table 2). Group 3 had a lower incidence of thoracic bleeding (10.3%) than groups 1 and 2 (31.5% and 25.7%, respectively, p=0.047) and a tendency toward less reoperation (10.3%) than groups 1 and 2 (29.0% and 17.1%, respectively, p=0.055). We also observed a tendency towards a lower incidence of neurological complications in group 3 (6.9%) than in groups 1 and 2 (22.8% and 26.3%, respectively, p=0.055) (Table 3). Patients in groups 2 and 3 presented with lower rates of stroke than those in group 1 (0 vs. 0 vs. 13.2%, p=0.01). No differences were observed between groups with respect to the occurrence of pulmonary reperfusion, acute kidney injury, or infectious complications.

The results of the multivariate analysis exploring variables associated with surgical complications, infectious complications, and in-hospital mortality are shown in Table 3. We found that being in group 3 was significantly associated with fewer surgical complications (OR 0.221 [95% CI 0.052–0.939], p=0.034 for the comparison of groups 1 and 3) and that high PASP was significantly associated with more surgical complications (OR 1.031 [95% CI 1.007–1.056], p=0.012). NYHA class III–IV was associated with more infectious complications than NYHA class I–II (OR 3.538 [95% CI 1.107–11.309], p=0.033).

Variables associated with higher in-hospital mortality were age (OR 1.06 [95% CI 1.02–1.10], p=0.047) and PVR (OR 1.00 [95% CI 1.00–1.01], p=0.024). From the receiver operating characteristic curve, after a partitioned analysis of the variables, patients aged ≥60 years were 6.2 times more likely to die and patients with PVR ≥860 dyn.s.cm^{-5} were 4.1 times more likely to die (Table 3).

Follow-up and 2-year mortality

Patients were evaluated 3–6 months after surgery, and >60% were in NYHA class I (Table 4). In the postoperative hemodynamic comparison, no significant difference was found in the parameters evaluated among the three groups. Of the 65 patients who underwent right heart catheterization, 58.5% developed residual PH.

The estimated survival probability at 24 months after surgery among the three groups was 70% for group 1, 77% for group 2, and 88% for group 3, and this difference was not significant (p=0.501).

Table 2. Postoperative outcomes.

Outcomes, n (%)	Group 1 (n = 38)	Group 2 (n = 35)	Group 3 (n = 29)	P*
Pulmonary reperfusion edema	5 (13.2%)	3 (8.6%)	5 (17.2%)	0.674
Acute kidney injury	7 (18.4%)	2 (5.7%)	4 (13.8%)	0.497
Surgical complications	13 (34.2%)	11 (31.4%)	3 (10.3%)	**0.035**
Bleeding	12 (31.5%)	9 (25.7%)	3 (10.3%)	**0.047**
Pericardial effusion	3 (7.8%)	6 (17.1%)	2 (6.9%)	0.991
Reoperation	11 (29.0%)	6 (17.1%)	3 (10.3%)	**0.055**
Infectious complications	12 (31.6%)	8 (22.9%)	5 (17.2%)	0.173
Mediastinitis	4 (10.5%)	2 (5.7%)	1 (3.5%)	0.249
Septic shock	10 (26.3%)	7 (20.0%)	5 (17.2%)	0.363
Neurologic complications	10 (26.3%)	8 (22.8%)	2 (6.9%)	**0.055**
Delirium	6 (15.7%)	8 (22.8%)	2 (6.9%)	0.384
Stroke	5 (13.2%)	0 (0.0%)	0 (0.0%)	**0.010**
In-hospital mortality	9 (23.6%)	8 (22.9%)	3 (10.3%)	0.192

*P value from the chi-square test (Mantel-Haenszel); p<0.05 was considered significant; n total number of patients.

Table 3. Significant variables in the multivariate model for surgical and infectious complications and in-hospital mortality.

Variable	OR (95% CI)	*P*
Surgical complications		
Group		
G1	Reference	
G2	0.755 (0.250-2.275)	0.574
G3	0.221 (0.052-0.939)	0.034
Estimated PASP (mmHg)	1.031 (1.007-1.056)	0.012
Infectious complications		
NYHA class		
I/II	Reference	
III/IV	3.538 (1.107-11.309)	0.033
In-hospital mortality		
Age (years)	1.061 (1.018-1.105)	0.047
PVR (dyn.s.cm^{-5})	1.002 (1.001-1.003)	0.024

OR: odds ratio; PASP: pulmonary artery systolic pressure; NYHA: New York Heart Association; PVR: pulmonary vascular resistance; p<0.05 was considered significant; CI confidence interval.

Table 4. Mid-term postoperative outcomes.

Variable	Group 1 (n = 29)	Group 2 (n = 27)	Group 3 (n = 26)	*P*
NYHA class, n (%)				0.385*
I	21 (75.0%)	16 (61.5%)	12 (63.1%)	
II	6 (21.4%)	9 (34.6%)	6 (31.5%)	
III	1 (3.5%)	1 (3.8%)	1 (5.2%)	
mPAP, mmHg (mean ± SD)	28 ± 9.7	30.4 ± 8.4	30.6 ± 14.3	0.661^{+}
RVP, dynas.s.cm^{-5} (mean ± SD)	248.3 ± 99.3	301 ± 257.6	317.7 ± 265.2	0.518^{+}
Residual hypertension, n (%)	13 (50%)	16 (72.7%)	9 (50%)	0.852*
Pulmonary vasodilator therapy, n (%)	1 (3.4%)	1 (3.8%)	2 (9.5%)	0.367*

NYHA: New York Heart Association; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance. *P value from the chi-square test (Mantel-Haenszel); $^{+}$P value from analysis of variance (ANOVA); n, patients with assessment; p<0.05 was considered significant.

DISCUSSION

The surgical treatment of CTEPH at InCor-HCFMUSP in Brazil started in 1981,[28] but only after 1990 that the operations were performed by the same surgical team. Within 10 years, the procedures were standardized, and this study analyzed the data of that period (from 2007 to 2016) and evaluated the influence of the interventions implemented on the procedures and their outcomes.

We had four main findings. First, we observed that surgical complications were less frequent after additional advances in surgical techniques were implemented. Thoracic bleeding occurred less in group 3 than in groups 1 and 2, and there was a tendency toward less reoperation and neurologic complications. Second, beyond being in group 3, we observed that high PASP was significantly associated with more surgical complications, and a higher NYHA class was associated with more infectious complications. Third, increasing age and PVR were significantly associated with in-hospital mortality. Finally, >60% of patients were in class I 3–6 months after surgery, but we did not observe differences in estimated survival probability among groups.

PEA remains the gold standard for CTEPH, and one of the factors that influence the post-surgical result is the experience of the referral center in disease management. The experience of clinicians, surgeons, and radiologists is essential for providing correct surgical indication, total removal of thromboembolic obstruction, and accurate management of the immediate and late postoperative period.[7,29,30] This level of experience was acquired by the local team at InCor-HCFMUSP, which probably also influenced the positive results of this study.

As CTEPH rarely occurs and difficult to diagnose, only a few specialized centers exist worldwide. The most important centers are found San Diego (USA), United Kingdom, France, and Germany (Europe).[15,29] In the last few years, some centers have disclosed their postoperative results,[5,6,9-15] which has helped us improve management by surgical, clinical, and postoperative teams.

In our study (10-year period), patients undergoing PEA in different time periods had similar baseline characteristics, clinical presentation, and functional and hemodynamic parameters. Approximately 50% of CTEPH patients had multiple risk factors the most frequent of which were smoking (20%), chronic venous insufficiency (13.7%), family history of venous thromboembolism or pulmonary embolism (10.7%), and these main variables were included in our univariate analysis. Their rates were comparable with those reported by Cannon et al.[15] and Pepke-Zaba et al.,[29] except for smoking, which was not mentioned. Significant PH was observed, with high mean values of PVR and mPAP, similar to previous reports.[12,15] During surgical procedures, the increase in total CPB time resulted from the standardization of the cooling, warming, and reperfusion times in groups 1 and 2. Thus, there was a progressive and significant increase in the cooling and warming times, and a reduction in the total systemic reperfusion time was probably associated with lower number of DHCA. Decreasing the number of DHCA was possible by increasing the mean time of each DHCA, allowing the safe removal of accessible thrombi from the pulmonary arteries. Previous studies[9,10] have shown advances in surgical techniques and in anesthetic procedures similar to those performed in our center, which also yielded improved outcomes.

Regarding surgical complications, operative field bleeding decreased significantly over time, similar to data from other authors.[12] In the multivariate analysis, being in group 1 was significantly associated with more surgical complications than being in group 3, which suggests the effectiveness of strategies for improvement such as the use of thinner polypropylene wires to perform arteriorrhaphy and biological glue. High preoperative PASP was associated with increased incidence of surgical complications, which may be related to the high pressure in damaged vessels and a higher incidence of bleeding. Note that the non-invasive measurement of PASP was performed up to 3 months from the date of surgery (84.67 ± 120.46 days), and invasive measurement of pulmonary pressures by right ventricular catheterization was performed after 3 months from the date of surgery (107.06 ± 194.03 days). Improvements in the arteriorrhaphy technique probably contributed to the lower occurrence of surgical complications. Regarding neurologic complications, stroke occurred in five patients in group 1, but not in groups 2 and 3. The results showed that the longer the DHCA time, the greater the incidence of temporary neurological complications.[12] In our study, the DHCA time did not reduce over time, but we observed an increase in the mean DHCA time with lower number of DHCA, which could have contributed to less permanent neurological complications, an original finding of this study. Additionally, the mortality rate in our center was comparable with that of previous studies that showed rates from 4.4% to 16%.[2,9,10,12,15] In our study, higher age and PVR were associated with in-hospital mortality, which might be explained by the development of microvascular disease and/or secondary vascular arteriopathy, contributing to worsening hemodynamic status and poorer prognosis after surgery.[5,6,10,11,13,14]

The postoperative functional evaluation through clinical evaluation at 3–6 months after hospital discharge showed that >94% of the patients were in functional class I–II, suggesting significant clinical improvement.[5,10,12,15] Although no significant differences were observed among the three groups in relation to hemodynamic parameters postoperatively, there was an important improvement in these values when compared with the preoperative values, similar to previous reports.[15]

We acknowledge two significant limitations of our study. First, as an observational single-center retrospective study, unmeasured confounding is always present, and our results should be interpreted as hypothesis-generating research. Second, improvements were performed in progressively reduced time intervals (60, 26, and 16 months for groups 1, 2, and 3, respectively); however, the number of PEA operations was similar among these time periods. These data revealed that a greater number of surgeries were performed with the same time interval (group 1, 0.6 surgeries/month; group 2, 5.9 surgeries/month; group 3, 1.8 surgeries per month).

Within the 10-year period, the InCor, a well-known Brazilian referral center for PEA surgery, promoted advances in anesthetic and surgical techniques, which are associated with a lower occurrence of surgical and postoperative complications. Further advances in the field are expected to progressively increase the quality of life and survival rate after this procedure.

ACKNOWLEDGMENTS

We are grateful to all patients and professionals involved in this research work. We would like to thank Editage (www.editage.com) for English language editing.

AUTHOR CONTRIBUTIONS

PGS: collaborated in the idealization of this work, construction of the database, data collection, data analysis, drafting the article and reviewing it. MT-F: collaborated in the direction of this work, from initial ideation to the final revision of Article. OFF: collaborated in the construction of the new surgery protocol, performing the surgeries, in the construction of the database, analysis and review of the article. TDA: collaborated in database construction, data analysis and revision of Article. DON: collaborated in the standardization of data collection and in the data collection itself. LMG: collaborated in data collection. FAG: collaborated in the construction of the new surgical protocol and in performing the surgeries using the new protocol. LAH:

collaborated to write the article and review it. FRBGG: collaborated in the construction of the new surgical protocol and in the anesthesia of the operated cases. FBJ: collaborated in the idealization of this work, construction of the database, data analysis, drafting the article and reviewing it.

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