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THERAPEUTIC ROLE OF SELECTIVE PREOPERATIVE EMBOLIZATION IN PATIENTS WITH PARAGANGLOMAS OF HEAD AND NECK

TERAPIJSKA ULOGA SELEKTIVNE PREOPERATIVNE EMBOLIZACIJE U PACIJENATA SA PARAGANGLIOMIMA GLAVE I VRATA

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Short title: Embolization of paraganglomas
Abstract

Background/Aim. are rare hypervascular neoplasms. The aim of this study was to present experience in treatment of paragangliomas with preoperative embolization. Methods. This is a retrospective cross-sectional study of 10 patients (7 women and 3 men; median age 55 years) with paragangliomas who were embolized before surgery. Results. Three had tympanicum paragangliomas, two carotid body, three jugulare and two jugulare-tympanicum paragangliomas. During the operation, 9 out of 10 patients didn't have bleeding which would require blood transfusion. One patient received 1130 ml of blood transfusion due to surgical complication. Conclusion. Adequate preoperative selective embolization of paragangliomas is essential in the preoperative preparation of these patients, because this strategy is feasible with low complications rates.

Key words: paragangliomas; embolization; blood transfusion; intraoperative blood replacement; imaging methods

Abstrakt


Ključne reči: paragangliom; embolizacija; transfuzija krvi; intraoperativna nadoknada krvi; metode vizualizacije
Paragangliomas (glomus tumors or chemodectoma) are rare hypervascular neoplasms. They arise from paraganglionic cells located in the walls of blood vessels or in specific nerves 1. They can be located in the carotid body (glomus caroticum) as the most common site 1, tympanic plexus (glomus tympanicum), located within the adventitia layer of the jugular bulb wall (glomus jugulare) and vagal nerve typically near the jugular foramen. The rare locations are trachea, larynx and nose cavity 2. In most cases these tumors are benign, slow-growing and locally destructive neoplasms, and a small percentage of tumors produce catecholamines 1, 3. The incidence of the paragangliomas is one per million people 3, where head and neck paragangliomas comprise three per cent of all paragangliomas 1. The majority of these tumors manifest in the fifth and sixth decade of life, predominantly in women 1, 3, 4.

Symptoms depend on the localization and type of paraganglioma. Glomus tympanicum causes conductive hearing loss, pulsatile tinnitus which is synchronized with the heart beat, and on the rare occasion otorrhea hemorrhage. Glomus jugulare tumors can cause jugulare foramen syndrome (paresis of cranial nerve IX and X), which is pathognomonic for this type of tumor. Paragangliomas may also present as hypertension and tachycardia if they are functional catecolamine–producing tumors (dopamine, norepinephrine, somatostatin), and rarely producing vasoactive intestinal polypeptide, calcitonin 2, 4.

Otoscopic examination shows characteristic reddish-blue pulsatile mass, localized behind the tympanic membrane 2. Classical radiography (X-ray) of the skull base can show widening of the foramen jugulare. Clinical diagnosis is confirmed by imaging methods - Ultrasound (US), computed tomography (CT) and Magnetic Resonance Imaging (MRI). Images with bone window are used for better visualization of the bone resorption caused by the glomus tympanicum. MRI is important for assessing the soft tissue involvement. T1 and T2 sequencies after gadolinium enhancement are mainly used, and sometimes fat-suppression sequences 1. Combination of CT and MRI is the gold standard for diagnoses of these tumors 1. Digital subtraction angiography (DSA) is very important and is used for the identification of tumor feeding arteries during embolization planning 1, 3, 4.

Therapy for the paragangliomas is total surgical resection, but because of its rich vascularization and high risk of hemorrhage, preoperative embolization is beneficial for reducing blood loss in the surgical field 1.
The aim of this study was to present experience in treatment of paragangliomas with preoperative embolization.

**Methods**

This is a retrospective cross-sectional study of 10 patients with paragangliomas who were embolized before surgery. We included all patients who were embolized before surgery of paragangliomas during the seven-year period, from 2012-2018. Patients with paragangliomas were treated with preoperative embolization using sclerosing agent (smaller particles from 100-300 microns) in the Institute of Radiology, Military Medical Academy, Belgrade, Serbia, and total surgical resection with a function preserving intent in Surgical Clinics Group in Military Medical Academy. We retrospectively analyzed the patient’s medical and imaging records.

After clinical examination as part of the diagnostics, a Multi Slice Computed Tomography (MSCT) examination was performed (64- and 128-slices MSCT, Aquilion system, Toshiba®; field of view 20 cm, section thickness 1 mm, contrast material volume 80 mL (joheksol), contrast material injection rate 3 mL/s). The MSCT examination was used to assess tumor size, relationship to surrounding anatomical structures and tumor vascularization.

After clinical diagnosis, patients were underwent imaging diagnosis with US (Figures 1A and 1B) and CT (Figures 2A, 2B and 2C) and preoperative endovascular embolization. Preoperative embolization started with a diagnostic digital subtraction angiography (DSA) via a transfemoral Seldinger approach. Right transfemoral access was obtained using a 6 Fr sheath-guiding catheter (Merit Medical). A guide wire (length 150 mm and 0.035 In) and 5 Fr diagnostic angiographic catheter (SIM II or JB Terumo® or Optitorque®) was then advanced into the common carotid artery on the side the tumor resided. After that, injection of radiocontrast joheksol (Omnipaque®, GE Healthcare Ireland limited, Ireland) by Avanti avast® pump (rate flow 6 mL/s) was used to visualize vascularization of tumor-digital subtraction angiography (DSA) (Figure 3A). Angiography was performed via the diagnostic catheter, placed into common carotid artery and other blood vessels, to determine the arterial feeders of the tumor.

After completion of the diagnostic angiogram, a 2.7 Fr microcatheter (Progreat®, Terumo interventional systems) was placed through the diagnostic catheter and advanced into selective branches of arteries where selective arteriograms could be performed for improved tumor visualization (Figure 3B). Smaller particles (100-300 microns, Bead Block®, BTG International...
Ltd, UK) was used for embolization. Beads were placed in one ml syringes which were attached to the microcatheter and injected in pulses that were synchronized with systolic heartbeat monitored by radioscopy (Figure 3C). If flow to the tumor was not diminished, larger bead sizes were incrementally selected until there was cessation of flow or reflux of contrast along the microcatheter. This technique was repeated for all branches that were large enough to accommodate the microcatheter. A final angiogram from the common carotid artery was performed to evaluate the degree of embolization and ensure patency of the internal carotid artery circulation (Figure 3D).

After embolization, paragangliomas were resected. A retro-auricular tympanic access route with canaloplasty was used for paragangliomas in the middle ear. Depending on the location and size of the paragangliomas, an endaural approach to the middle ear with additional mastoidectomy and myringoplasty was performed. Ossicular reconstruction was performed if required.

The surgical technique for carotid body paragangliomas included precise anatomic dissection and vascular control prior to attempted tumor excision. The dissection to remove the carotid body paraganglioma was carried out along the arterial subadventitial plane to allow for complete local tumor excision, as well as preservation of critical vascular structures (Image 1). Postoperative care included close pharmacologic control of systolic blood pressure and postoperative clinical neurologic evaluation.

Complete statistical analysis of data was performed using the statistical software package, PASW Statistics 18 [SPSS (Hong Kong) Ltd., Hong Kong]. All variables were presented as frequency of certain categories. Chi-square test was used for analyzing the significance of differences of categorical variables. Continuous variables were presented as median and interquartile range (IQR) and were compared using nonparametric Mann-Whitney U test. Distribution normality was tested using the Shapiro-Wilk Normality Test (number of subjects was < 50). All analyses were estimated at p < 0.05 level of statistical significance.

Ethical Statement: All procedures performed in our study with human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration or comparable ethical standards.
Results

We analyzed data from 10 patients with paragangliomas (7 women and 3 men), median age 55.0 years, with IQR from 49.75 to 61.25 years who were treated with embolization before surgery (Table 1). Female patients were statistically significantly older in comparison to males (Mann-Whitney test; p=0.017) (median age of males and females was 49.0 and 59.0 years, respectively).

Three patients had glomus tympanicum, two with carotid body, three with jugulare and two with jugulare-tympanicum glomus tumor (Table 1). Seven patients had right side paraganglioma, while two patients had left side tumor and one patient had tumors on both side. Largest tumor diameter median was 29.0 mm with IQR from 24.0-32.5 mm. During the operation 9 out of 10 patients didn't have bleeding which would require blood transfusion. One patient who had jugulare-tympanicum glomus tumor received 1130 ml of blood transfusion because of the hemorrhage from carotid sinus during the surgical intervention.

Table 2 shows the clinical characteristics of patients treated in this study. Most patients with paragangliomas had arterial hypertension (six patients) and hearing impaired (also six patients). Five patients had tinnitus, and six patients had pulsations in the ears. Only three patients had ear pain. On MSCT examination, five patients had osteolysis.

Median number of tumor feeder branches was 1.5 (Table 2). Five tumors had one feeder branch, and five tumors had two or three feeder branches. In our patients we showed that is embolization had the extent of devascularization of the paragangliomas 100% in all patients.

Discussion

Paragangliomas are rare hypervascular neoplasms, whose surgical resection is at great risk for intraoperative bleeding. Therefore, preoperative reduction of perfusion of these tumors with embolization is very important for reducing the risk of bleeding, both for the patient and for the operation performed by surgeon.

Our results show that preoperative embolization using small sized beads (100-300 microns) with superselective access to arterial feeders, results in almost complete tumor devascularization by 100% patients.
The results from our study in 10 patients showed that devascularization eliminated the need for intraoperative blood transfusion. An exception was one patient who required significant blood transfusion during surgery (1130 ml) due to the hemorrhage from carotid sinus.

Surgical resection of paragangliomas can be complicated due to massive bleeding because of their high vascularity. With the evolution of preoperative planning, surgical techniques, and diagnostic evaluations, the risk of artery injury are minimal. The risk of injury to the carotid artery following treatment of carotid body tumors is size specific: tumors larger than 5 cm are likely to require carotid reconstruction. Unlike jugulo-tympanic paragangliomas and carotid body tumors, vagal paragangliomas are not closely associated with the carotid artery, although the internal carotid artery may be involved in its petrous portion in advanced disease. Rarely, injury may occur, even with adequate surgical exposure and microsurgical technique. If the patient is at high risk for vessel injury within the petrous carotid portion and balloon occlusion testing has been safely and satisfactorily performed, then the surgeon may consider permanent preoperative occlusion of the carotid distal to the tumor.

Preoperative embolization of paragangliomas is a very safe adjuvant therapy before surgical resection. Bead embolization dramatically reduced tumor vascularity. The classic angiographic appearance of a paraganglioma is that of a hypervascular mass with robust feeding arteries and intense tumor blush. Successful embolization hinges upon occlusion of all feeding vessels, based upon DSA. A delay of 1-2 days between embolization and total surgical resection allows time for local edema or inflammation to resolve with minimal time for revascularization or recruitment of feeding arteries. The effectiveness of embolization hinges upon occlusion of the feeding tumoral vessels of paragangliomas. The catheterization technique should be superselective, aiming only for feeding vessel of the paraganglioma.

Other studies show reduction of 60% to 68% intraoperative blood loss in patients who underwent preoperative embolization when compared with those who did not. In the study by White et al. it was shown that post-embolization angiography revealed an average decrease in blood flow to tumor of 75%. An 80-90% reduction in tumor vascularity is often obtained. The intraoperative blood loss for each tumor type was 289 ml for carotid body, 243 ml for glomus vagale, and 1018 ml for glomus jugulare. Larouere et al. showed that the average blood loss for the embolized patients was 650 ml (range from 500-1000 ml). In the nonembolized patients, the average blood loss was 1375 ml (range from 1200-1725 ml).
Jackson et al. suggested that preoperative embolization in the patients with paragangliomas leads to a decrease in intraoperative blood loss and operative time. The mean estimated blood loss among the patients with embolization was 0.52 standard deviations lower (0.77 to 0.28 lower) than that of patients without embolization.

Therapy for paragangliomas is total surgical resection, but because of its rich vascularization and high risk of hemorrhage, preoperative embolization is beneficial for reducing blood loss in the surgical field. On the other hand, for small localized glomus tympanicum tumors, transcanal endoscopic ear surgery is a favorable surgical method. These tumors present high bleeding risk during resection. Embolization can be curative with surgical resection, palliative or supportive, but the main reason for this procedure is to detect and obliterate the abnormal vascular structures of the tumor. This way it is possible to decrease the vascularity and volume of the tumor, and make it safer for the surgery.

Limitations of this study: Unlike other reported studies, there is no control group of non-embolized tumors to compare embolization efficacy as manifest by operative blood loss. We also had a small number of these patients.

Conclusion

Adequate preoperative selective embolization of paragangliomas is essential in the preoperative preparation of these patients, because this strategy is feasible with low complications rates.

REFERENCES


### Table 1

**Demographic and clinical characteristics of patients with paragangliomas**

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Fig. 1- Ultrasonic finding- heteroechoic, dominant hyperechoic change, relatively clearly limited: A- Anteroposterior x craniocaudal diameter about 25 x 27 mm; B- lateral-lateral diameter about 19 mm
Fig. 2- MSCT findings of the neck- hypervascular expansive lesions at the level of bifurcation of common carotid artery which moves the external and internal carotid arteries: carotid glomus: A- coronal; B- sagittal; C- axial slices
Fig. 3- A: Angiography at the level of bifurcation of common carotid artery by 5 Fr diagnostic angiographic catheter (Terumo®) showed hypervascular tumor change, which moves the external and internal carotid arteries: carotid glomus; The tumor is dominantly vascularized from the pronounced, tortuous ascending pharyngeal artery; B: Selective catheterization of external carotid arteries through the diagnostic catheter and supraselective catheterization of ascending pharyngeal artery by Progreat (Terumo®) microcatheter; C: Control angiography through microcatheter after the application of embolization agent (Bead Block®) size 100-300μm; D: Control angiography through the diagnostic catheter in the common carotid artery after embolization with complete tumor devascularization
Image 1. Surgical resection of carotid body tumor; ACI, internal carotid artery; ACE, external carotid artery, ACC, common carotid artery