

Key perspectives on stenting of symptomatic vertebral artery stenosis, resident involvement in neurosurgery, antithrombotic therapy following sellar and parasellar tumor resection, and radiosurgery for vestibular schwannomas

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Received: 04 November 15 Accepted: 27 November 15 Published: 07 October 16

Key Words: Antithrombotic therapy, radiosurgery, resident, tumor, vertebral artery stenosis, vestibular schwannomas

STENTING VERSUS MEDICAL TREATMENT IN PATIENTS WITH SYMPTOMATIC VERTEBRAL ARTERY STENOSIS: A RANDOMIZED OPEN-LABEL PHASE 2 TRIAL^[1]

Study Question: In patients with symptomatic atherosclerotic vertebrobasilar artery stenosis, is stenting in addition to best medical treatment better than best medical treatment alone?

The objective of this study was to assess the safety and feasibility of stenting plus best medical treatment compared with best medical treatment alone in patients with symptomatic atherosclerotic vertebrobasilar artery stenosis of at least 50%. The patient population comprised patients from seven hospitals in the Netherlands from 2008 to 2013. Key inclusion criteria were a vertebrobasilar transient ischemic attack (TIA) or ischemic stroke in previous 6 months and intra- or extra-cranial atherosclerotic

vertebrobasilar artery stenosis of >50%. Primary outcomes included vascular death, myocardial infarction (MI), and ischemic stroke within 30 days. The study was a 1:1 randomization to stenting plus best medical treatment or best medical treatment alone. The outcomes were assessed by a blinded endpoint committee, but neither patients nor investigators were blinded. The stent used was at the discretion of the interventionalist, and if stent placement was not feasible, percutaneous transluminal angioplasty (PTA) alone was performed. Best medical therapy was at the discretion of treating neurologist.

The results were reported as an intention to treat analysis: Of 115 patients, 57 patients were assigned to the stenting group and 58 patients to the medical group. Fifty of the

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How to cite this article: Kan P, Bohnen A, Germanwala AV, Pelargos P, Choy W, Yang I, et al. Key perspectives on stenting of symptomatic vertebral artery stenosis, resident involvement in neurosurgery, antithrombotic therapy following sellar and parasellar tumor resection, and radiosurgery for vestibular schwannomas. *Surg Neurol Int* 2016;7:S733-6.

<http://surgicalneurologyint.com/Key-perspectives-on-stenting-of-symptomatic-vertebral-artery-stenosis,-resident-involvement-in-neurosurgery,-antithrombotic-therapy-following-sellar-and-parasellar-tumor-resection,-and-radiosurgery-for-vestibular-schwannomas/>

Access this article online	
Quick Response Code:	Website: www.surgicalneurologyint.com
	DOI: 10.4103/2152-7806.192514

57 (88%) patients actually had stenting or PTA. Composite outcome (vascular death, MI, or stroke within 30 days) occurred in 3 of 57 (5%) patients in the stenting group versus 1 of 58 (2%) patients in the medical treatment group. Of the patients with intracranial stenosis, 2 of 9 patients reached the primary outcome versus 0/10 in the medical group. Stroke in the territory of the symptomatic vertebral artery occurred in 7 of 57 (12%) patients in a stenting group versus 4 of 58 (7%) patients in the medical group and the difference persisted at the final follow-up at 3 years. The composite outcome on the final follow-up was similar: 11 of 57 (19%) patients in a stenting group versus 10 of 58 (17%) patients in the medical treatment group.

Perspective: Vertebrobasilar TIA or ischemic stroke is associated with atherosclerotic disease in the vertebral or basilar artery. Similar to carotid disease, the presence of symptomatic vertebrobasilar atherosclerotic stenosis is associated with increased risk of recurrent vertebrobasilar stroke.^[6] The intracranial vertebrobasilar disease may represent a higher recurrent stroke risk than the extracranial vertebral disease.^[2] With the advent of stenting technology, endovascular treatment of symptomatic vertebral artery stenosis with PTA and stenting is increasingly used as a therapeutic intervention but unlike in extracranial carotid artery disease and intracranial atherosclerotic disease, the role of stenting in atherosclerotic vertebrobasilar artery disease is not well-established.

In the current study, stenting plus best medical therapy appears to have a worse outcome compared with best medical therapy alone on patients with symptomatic vertebrobasilar atherosclerotic disease of at least 50%. This is in contrast to atherosclerotic carotid artery disease where intervention is beneficial. The strength of the study includes its design (a randomized-controlled study with outcomes blindly adjudicated), its size (the largest completed randomized clinical trial in patients with symptomatic vertebrobasilar disease), and novelty (the first randomized trial to report on rate of recurrent vertebrobasilar stroke on long-term follow-up in patients with symptomatic vertebral artery stenosis suitable for stenting). The weakness of the study includes its premature stoppage because of the lack of funding (thus insufficiently powered for definitive conclusions); the fact that best medical therapy was not standardized, and there was variability in endovascular devices employed.

Summary Written by: Peter Kan, MD, MPH

IMPACT OF RESIDENT INVOLVEMENT IN NEUROSURGERY: AN ANALYSIS OF 8748 PATIENTS FROM THE 2011 AMERICAN COLLEGE OF SURGEONS NATIONAL SURGICAL QUALITY IMPROVEMENT PROGRAM DATABASE^[4]

Study Question: Does neurosurgical resident involvement

during surgical procedures affect the overall patient postoperative outcome?

Researchers utilized the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to retrospectively review 8748 neurosurgical cases in 2011 which included resident involvement. Cases were analyzed based on the presence of attending alone (4219) versus attending and resident (4529 cases), and primary outcomes were measured (overall/surgical/medical complications, reoperation, mortality, and unplanned readmission, all within 30 days). Propensity scoring analysis using demographics, co-morbidities, and perioperative details helped identify the probability of resident involvement and was incorporated into the logistic regression model to adjust for confounding variables and reduce bias. The impact of resident involvement on each primary measure was investigated via multivariate regression analysis. Furthermore, only qualifying variables (based on univariate analysis) were included in the regression models. The univariate analysis comparing outcomes found that resident involvement was significantly correlated with the incidence of postoperative complications in all measures. However, when accounting for selected risk factors and propensity score, the risk was still increased but did not reach significance, suggesting that inherent baseline differences contribute to the postoperative risk increase.

Perspective: This retrospective study is a first look into the role of residents in neurosurgical cases. There are smaller reports of safe resident involvement; however, these looked at specific surgical procedures. Previous reports from other specialties, such as general surgery and vascular, revealed similar data. The advantages of the study are the use of a nationally validated database to provide a large, multi-centered sample of patient cases. Multiple disadvantages are present, though. The NSQIP does not report extent of resident role within the case, nor does it identify the postgraduate year. The data suggest that resident cases are of longer duration, increasing morbidity postoperatively, which could be related to the experience of the assisting surgeon. It is also known that tertiary training centers often receive tougher surgical cases and sicker patients than community centers. By adjusting for relative value unit's, this is somewhat accounted for; however, much of the surgical complexity can be missed by coding alone and, therefore, is not completely represented in the multivariate analysis. In addition to more complex cases, patients at resident training centers are often less healthy than those undergoing elective cases at other centers, providing a greater challenge to minimize postoperative complications. In addition, residents are more likely to be involved in emergent cases, including trauma. The nature of these cases leaves patients in a critical situation and extremely high risk for added comorbidity and mortality.

Overall, when adjusting for confounding factors, cases in which residents are involved do have higher complication rates; however, not to a significant degree. Training centers are a safe place for both educating future surgeons and providing good patient care. There is, though, inherent risk at such institutions as they often handle difficult cases and sicker patients. It would be interesting to assess for complications >30 days postsurgery and for case specific complications such as cerebrospinal fluid (CSF) leak, frontalis palsy, and peripheral nerve palsy.

Summary Written by: Angela Bohnen, MD

SELLAR AND PARASELLAR TUMOR REMOVAL WITHOUT DISCONTINUING ANTITHROMBOTIC THERAPY^[7]

Study Question: Is there an increased risk of bleeding from transsphenoidal surgery when operating on patients without fully discontinuing antithrombotic therapy?

The authors review a retrospectively acquired database of 15 consecutive adult patients on antithrombotic therapy, held only on the day of surgery, with sellar and parasellar masses. These patients were treated by the sublabial transsphenoidal approach by a single surgeon at a single institution over roughly a 5-year period. Data reviewed included an antithrombotic agent, lesion histology and volume, blood loss, operation time, cavernous sinus entry, the extent of resection, and hospital course. A contemporaneous group of 15 patients undergoing the sublabial transsphenoidal approach by the same surgeon was used as a control.

Within the patient group on antithrombotic therapy, eight patients were solely on aspirin therapy while four patients had elevated international normalized ratio suggesting (although not documented) the use of warfarin. All treated lesions were extra-arachnoidal, including nine adenomas and four Rathke's cleft cysts. The cavernous sinus was entered in four patients. Averages for lesion volume estimated blood loss and time of operation were 2.45 ml, 255 ml, and 167.8 min, respectively. A comparison of these values to those in the control group revealed similar results. Gross total resections were performed in nearly all patients in both groups. No patient in either group had clinically significant bleeding or developed a neurological deficit. All patients were discharged on the postoperative day 12.

Perspective: There was no statistically significant difference in blood loss, operating time, or extent of resection between the two groups. These results suggest that transsphenoidal approaches for resection of extra-arachnoidal lesions, even with entry into the cavernous sinus, can be performed safely and effectively without discontinuing the use of antithrombotic agents. Limitations of this study include a small number of

patients and average lesion size. The manuscript does not describe the reason for surgery, intraoperative CSF leak rate, method of dural reconstruction or long-term follow-up. In addition, an explanation for keeping every patient in the hospital for 12 days is not provided.

Increasing numbers of patients are being prescribed antithrombotic medication for abnormal heart rhythms, cardiac valve procedures, deep venous clots, intracranial stenoses, malignancy related syndromes, and coronary stents. Some of these patients will develop neurosurgical pathology that demands clinical attention. Given the high rate of visual deficits and endocrine dysfunction with skull base tumors, the benefit of symptomatic improvement from neurosurgical intervention is currently balanced with the risk of discontinuing medical antithrombotic therapy. This study will hopefully serve as an impetus to launch randomized-controlled trials that may provide stronger conclusions. These results, however, cannot be extrapolated to intra-arachnoidal lesions given the presence of intracranial vasculature within the subarachnoid space.

Summary Written by: Anand V. Germanwala, MD

GAMMA KNIFE RADIOSURGERY FOR VESTIBULAR SCHWANNOMAS: EVALUATION OF TUMOR CONTROL AND ITS PREDICTORS IN A LARGE PATIENT COHORT IN THE NETHERLANDS^[3]

Study Question: What are the tumor control rates and the complication rates for vestibular schwannomas (VSs) treated with gamma knife radiosurgery (GKRS)?

The authors^[3] conducted a retrospective analysis of 420 patients who were treated with GKRS as primary treatment for unilateral VS at the Gamma Knife Center, a nationwide tertiary referral hospital, in Tilburg, The Netherlands, between July 1, 2002, and November 1, 2010. Patients were included in the study cohort if they were not treated for VS prior to receiving GKRS, they did not have neurofibromatosis type 2, and they had follow-up data available. The primary analysis of the study was to determine the tumor control and complication rates following GKRS while the secondary analysis was the determination of predictors of VS tumor control. The authors also conducted a subgroup analysis on patients with serviceable hearing and available audiograms to determine the rate of hearing preservation following GKRS. Four hundred and twenty patients were included in the primary and secondary analyses, while 71 patients were examined in the subgroup analysis for hearing preservation.

The authors reported that 286 patients were treated with the Leksell Gamma Knife 4C and 134 patients were

treated with the Leksell Gamma Knife Perfexion. Patients were treated with a dose of 11–13 Gy to the isodose covering 90% of tumor volume, resulting in an ~11 Gy marginal dose. The mean age of the study cohort was 57.6 ± 12.7 years, and the median follow-up time was 5.1 years with an interquartile range of 4.0–7.0 years. The authors defined treatment failure as the need for additional treatment with GKRS, microsurgery, or both. The decision for additional treatment was based on tumor progression observed on consecutive imaging. GKRS treatment resulted in a tumor control rate (absence of treatment failure) of 89.3% with actuarial 5- and 10-year control rates of 91.3% and 84.8%, respectively. The median time to treatment failure was 4.2 years (range 1.6–7.0 years) for those requiring secondary GKRS and 3.1 years (range 0.3–5.1 years) for those requiring microsurgery. The significant predictor for tumor control following primary GKRS was tumor volume ($P < 0.01$). Patient age, VS characteristics (cystic/noncystic), and marginal dose were not significant predictors of VS tumor control. Further, the authors found that the actuarial 5-year tumor control rate was higher in tumors $<0.5 \text{ cm}^3$ (94.1%) than in tumors $\geq 0.5 \text{ cm}^3$ (90.0%) (log-rank test, $P < 0.05$) as well as significantly higher in tumors $<6 \text{ cm}^3$ (92.2%) compared to tumors $\geq 6 \text{ cm}^3$ (80.7%) (log-rank test, $P < 0.05$). In regards to complications following GKRS treatment, the authors reported 3.1% of patients had new/increased permanent trigeminal neuropathy, 1.0% had new/increased permanent facial weakness, 1.2% had new/increased hydrocephalus requiring shunting, 13.2% had new/increased tinnitus, and 14.8% had new/increased vertigo symptoms. In the subgroup analysis, the authors reported a hearing preservation rate of 60.6% with an actuarial 3- and 5-year hearing preservation rate of 65% and 42%, respectively.

Perspective: Stereotactic radiosurgery has grown in its acceptance as a viable treatment for VS. The currently accepted marginal dose for effective treatment and control is 12.0–13.0 Gy.^[5,8] As the authors have pointed out for their study, the actuarial 5-year VS tumor control rate is lower than that reported for comparable studies which report control rates ranging from 93% to 97%, though the authors did perform a statistical evaluation to determine if this difference in control rates insignificant. The complication rate and hearing preservation rate between this and comparable large studies are similar. As the authors of the article expertly described, the comparability of the results of this study with other similar studies is limited based on the following: The definitions of treatment failure and complications are not uniform (especially for objectively rated complications such as pain or tinnitus), not all studies report actuarial

figures, and the decision for additional treatment is often based on subjective/nonuniform criteria. Despite these limitations in comparability, it is interesting that the tumor control rate at 11 Gy marginal dose is lower than the control rate at 12–13 Gy without any corresponding decreasing in the complication rate. This appears to point to a marginal dose of 12–13 Gy being the limiting dose that can be given to VS tumors without negatively affecting the control rate. The authors state that since 2011 their center has increased the marginal dose given to VS tumors. Once there is sufficient follow-up data, a future comparison of outcomes and complications of these patients receiving increased marginal dose compared to those presented in this study who received 11 Gy marginal dose will provide a more definitive answer as to the optimum marginal dose for VS. In the meantime, it appears that 12–13 Gy is the optimal marginal dose giving minimal complications without sacrificing tumor control.

Summary Written by: Panayiotis Pelargos, BS and Isaac Yang, MD

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: A randomised open-label phase 2 trial. *Lancet Neurol* 2015;14:606-14.
- Gulli G, Marquardt L, Rothwell PM, Markus HS. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: Pooled data analysis from prospective studies. *Stroke* 2013;44:598-604.
- Klijn S, Verheul JB, Beute GN, Leenstra S, Mulder JJ, Kunst HP et al. Gamma knife radiosurgery for vestibular schwannomas: Evaluation of tumor control and its predictors in a large patient cohort in The Netherlands. *J Neurosurg* 2015;2:1-8.
- Lim S, Parsa AT, Kim BD, Rosenow JM, Kim JY. Impact of resident involvement in neurosurgery: An analysis of 8748 patients from the 2011 American College of Surgeons National Surgical Quality Improvement Program database. *J Neurosurg* 2015;122:962-70.
- Lunsford LD, Niranjan A, Flickinger JC, Maitz A, Kondziolka D. Radiosurgery of vestibular schwannomas: Summary of experience in 829 cases. *J Neurosurg* 2005;102 Suppl:195-9.
- Marquardt L, Kuker W, Chandratheva A, Geraghty O, Rothwell PM. Incidence and prognosis of $> \text{or} = 50\%$ symptomatic vertebral or basilar artery stenosis: Prospective population-based study. *Brain* 2009;132(Pt 4):982-8.
- Ogawa Y, Tominaga T. Sellar and parasellar tumor removal without discontinuing antithrombotic therapy. *J Neurosurg* 2015;123:794-8.
- Petit JH, Hudes RS, Chen TT, Eisenberg HM, Simard JM, Chin LS. Reduced-dose radiosurgery for vestibular schwannomas. *Neurosurgery* 2001;49:1299-306.