

Emerging Trends & Techniques Related to Treatment in Patients with intra – Conal Cavernous Hemangioma of the Orbit (OCH)/orbital Cavernous Malformation (OCVM) and Treatment-related Complications, A Systematic Review

Saniya Seher, Shenel A.Khan, Sonya Mounien, Vivig Shantha Kumar, Rasheek Nerella, Basim Shaman, Dev Patel, Jabez John, Ranita Bodepudi, Safeera Ahmed
Journal for International Medical Graduates

Abstract

Orbital Cavernous venous malformation (OCVM), formerly known as cavernous hemangioma of the orbit (OCH) is a frequent benign, slow-growing, non-distensible venous malformation with ISSVA classification which classifies it into different types. This research has employed randomized controlled trials (RCTs), case reports, retrospective case studies, systematic reviews, and cohort studies to evaluate the treatment choices for OCVM and its consequences. The goal of this review is to analyze the comprehensive therapies used for OCVM. For our literature search, we looked at PubMed/MEDLINE, PubMed Central and Cochrane across six years (from 2016 to 2021). Using the Cochrane risk of bias quality assessment tool, the found studies underwent a quality check (modified Cochrane RoB 2). For the reporting of this systematic review, we adopted preferred reporting items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria and included a total of 10 papers. The majority of research confirmed the accuracy of OCVM detection using MRI and CT. To evaluate the effects of the intervention on OCVM more precisely, more trials with a longer follow-up time are needed. This study will explore recommendations and guide orbital surgeons, regardless. It will aid in the development of future strategies involving both invasive and noninvasive procedures to close the surgical and complication gap.

Introduction

Cavernous venous malformation (CVM), formerly known as cavernous hemangioma of the orbit (OCH) is a frequent benign, slow-growing, non-distensible venous malformation, may present with proptosis with 2mm progression reported each year and more prevalent in women aged 30-50 more typically involve intra-Conal region. Evidence suggests that after lymphoid tumours and orbital inflammatory syndrome, CVM ranked third among 1264 orbital lesions in a survey of adult patients referred to an eye oncology clinic. International Society for the Study of Vascular Anomalies, classification of Vascular Anomalies of 2018 classified OCVM into three major categories. Type one is encapsulated, non-expandable (OHM), the second

type is non-encapsulated expandable also known as (Orbital Varix) and the third is the diffuse expandable and invasive lesions (OVM) [1,2,3,4,5]. Treatment of intra-conal CVM is challenging. There are recognized external surgical methods for operating on the orbit including osteotomies with or without external orbitotomies [3]. Gamma knife radiosurgery (GKRS) is a representative technique of stereotactic radiosurgery [6,7], an endoscopic endo-nasal transsphenoidal approach (EETA) [8] and resection of an optochiasmatic cavernoma via a transsphenoidal approach are examples of noninvasive techniques. Purely endoscopic trans-nasal removal of intra-Conal orbital hemangiomas with the assistance of a dedicated cryoprobe is another technique [2,4]. Trans-septal suture retraction for endoscopic endonasal surgery [9] clinically the efficacy of 360-degree minimally invasive endoscopic surgery in patients with orbital intra-Conal tumours [10]. This Systematic review will discuss Invasive and noninvasive techniques, their complication rates and visual outcomes.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, 2020, served as a guide for conducting this systematic review, and they were strictly followed (11). The question created intended to highlight various approaches to treating cavernous hemangioma.

Search Strategy

To find the publications for this research paper, we used two important databases: PubMed, which by extension includes content from MEDLINE and PubMed Central (PMC) (Medical Literature Analysis and Retrieval System Online). Additionally, Science Direct has been used to raise the yield. To identify the required articles, we generated a Medical Subject Headings (MeSH) strategy using specific keywords and Booleans. These included: ("Hemangioma, Cavernous/embryology"[Mesh] OR "Hemangioma, Cavernous/epidemiology"[Mesh] OR "Hemangioma, Cavernous/microbiology"[Mesh] OR "Hemangioma, Cavernous/surgery"[Mesh] OR "Hemangioma, Cavernous/therapy"[Mesh]). The

developed MeSH strategy was then entered into the PubMed search engine, which returned articles that were related to the MeSH strategy but not exclusively. Then, based on the titles and available abstracts, articles were found and screened. Additional duplicates were found, and they were eliminated from our collection of articles. Before being picked for the study, the chosen papers underwent additional screening using our predetermined inclusion/exclusion criteria and were evaluated for quality.

Inclusion and Exclusion Criteria

Meta-analyses, systematic reviews, retrospective case reviews, retrospective studies, and case reports were among the articles chosen for this systematic review. These publications included ones that were published throughout six years (from 2016 to 2021), had patient populations older than 18, were published exclusively in English, and involved both sexes. Papers were eliminated if a) a full-text article was not accessible, b) a paper was considered to be grey literature, or c) a paper did not directly relate to the study subject under consideration.

Assessment of Study Quality

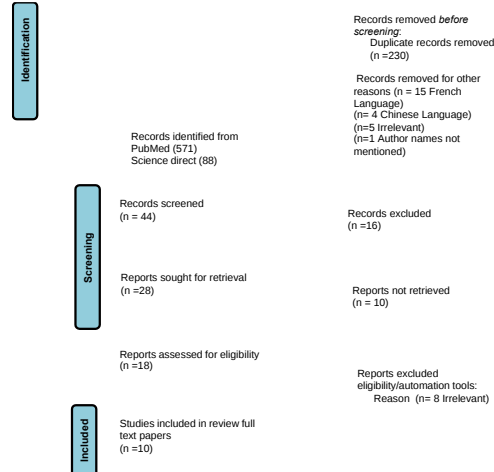
All remaining papers were evaluated for quality using the Cochrane risk-of-bias assessment tool following putting in our inclusion/exclusion criteria. Each paper's bias risk might be classified as high, low, or minor risk concerns under RoB 2. Amstar checklist, JB check tool, New Castle Ottawa and relevant quality appraisal tools were used.

Results

The MeSh technique described in the method section was used to find out total of 659 articles. After applying filters (human species, English language, and 18+ age group, publication dates from January 1, 2016, to December 2021), it was reduced to 44, from which duplicates were manually eliminated. After that, the publications were filtered according to how closely the title and abstract linked to the research issue. The eligibility requirements and availability of the full text were also used to screen papers. A quality evaluation was completed for a total of 10 papers that were determined to be eligible for review.

Figure 1 shows a flow diagram for PRISMA; however, Table 1 represents included study types, procedures, and associated complications.

Fig 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Author	Year of Publication	Purpose of study	Study design	Number of Patients	Intervention studied	Anatomical Location	Complications.
Luigi Calandriello, et. Al	2017	Cavernous venous malformation (Cavernous hemangioma) of the orbit: Current concepts	Literature Review	403	Anterior orbitotomy Lateral and transcranial orbitotomy	Intra-Conal Extra-Conal	Eye lid hematoma, mydriasis, direct optic nerve injury resulting in visual loss, and arterial occlusion
Riccardo Lenzi et al ^[2]	2015	Purely endoscopic trans-nasal management of orbital intra-Conal cavernous hemangiomas	Systematic review	17	Trans-nasal endoscopic resection	Intra-Conal orbital lesion affecting inferior-medial quadrant	Post-operative nasal crusting, acute orbititis, double vision sinking of the eyeball into the orbital cavity
Pedro Claudio Set et al ^[3]	2019	Orbital cavernous hemangioma; outcome managed surgically	Retrospective case review	76	Lateral orbitotomy with or without lateral orbital rim section	Intra-Conal	Early post-operative complications, linked with surgical trauma superior palpebral swelling, subconjunctival haemorrhage, chemosis and lateral rectus trauma
Paolo Castelnovo et al ^[4]	2019	Endoscopic Trans-nasal Cryo-Assisted Removal of Orbital Cavernous Hemangiomas	Case report	2	Trans-nasal intraorbital endoscopic procedure with add-on the probe	Intra-Conal	Nasal crusting
Diego Sranese et al ^[5]	2021	Risks and Benefits of Surgical Orbital Cavernous Venous Hemangioma: Factors influencing the Outcome	Cohort	164	Lateral or anterior orbitotomy	Intra-Conal, Extra conal involving muscle	Irreversible visual loss 1.2%, VA deterioration 3% to 32%, Tonic pupil with poor accommodation in 4%, Proptosis 1%, Diplopia 3%

Joel Caballero-Garcia et al. [10]	2021	Minimally Invasive 360-Degree Approach to Intraconal Orbital Tumors	Interventional case series	22	Minimally Invasive 360-degree endoscopic surgery	Intra-conal	Related to the frontotemporal parietal approach are cerebrosplinal fistulae or meningitis
Matthew Kim et al. [9]	2020	Trans-septal suture retraction for endoscopic orbital surgery	Case Report	1	Trans-septal suture retraction	Retro bulbar intra conal mass with adjunct extra-conal extension	A traction suture embarks lower risk of significant bleeding in low-flow vascular lesions
Xiaoli Meng et al. [8]	2017	Endoscopic Endonasal Trans-sphenoidal Approach for the Removal of Optochiasmatic cavernous	Case Report Literature Review	1	Endoscopic Endonasal Transsphenoidal	Optochiasmatic cavernoma	Postoperative cerebrospinal fluid leak
Won Jae Lee et al. [7]	2020	Stereotactic radiosurgery for orbital cavernous venous malformation	Retrospective	14	GKRS	Intra Conal	Not discussed
Stephanie Ming Young et al. [6]	2019	Orbital apex venous cavernous malformation with optic neuropathy: treatment with multi-session gamma knife radiosurgery	Retrospective cohort study	12	GKRS	Orbital apex	Not discussed

Table 1: Characteristics of included studies GKRS: Gamma knife radiosurgery

Discussion

Cavernous haemangioma of the orbit (OCH) is a benign usually intra-conal orbital lesion but can be found in extra-conal areas such as orbital apex muscles and rarely optic chiasma with a high frequency of occurrence in women of 3rd to 5th-decade studies suggest it ranks third [1-5] Treatment involve Surgical excision, particularly lateral orbitotomies there are non-invasive methods to remove it to prevent intraoperative and postoperative complication. We intend to assist orbital surgeons and researchers in filling this data gap in the future to enhance patient outcomes. This systematic review offers thorough evidence of treatment efficacy in OCH. Most individuals who had proptosis before surgery exhibited improvement in VA six months following surgery. The surgical outcome in terms of VA improvement appeared to be influenced by the size of the tumour, preoperative VA, and aberrant funduscopy.

The primary imaging modalities used to pinpoint the location of the OCMV and its relationship to other orbital tissues. In the majority of the included studies CT- scan and MRI Contrast-enhanced were the main modalities

to identify OCMV anatomical location and its relationship with orbital structures. Additionally, the literature showed partially excised OCMVs show no recurrence over time.

The surgical team's experience with a particular method plays a vital role in this decision.

It has been demonstrated that OCH-related symptoms are typically recoverable until the axial length is permanently altered or complete loss of the optic nerve, resulting in irreversible visual impairment in all cases with confirmed pathology results of OCH. In this systematic review we comprehend the treatment approaches their pros and cons and patient long-term safety related to procedures.

A) Conservative approach

Due to the inherent risks of all surgical treatments, and postoperative morbidity, which may include the worsening of pre-existing deficits and the development of new ones, regular clinical and radiological follow-up is recommended in asymptomatic or moderately symptomatic cases.

1) Conventional surgical approach for Intra-Conal/Extra-Conal lesions not involving Orbital apex

Accounts for 60% of cases overall surgical approaches include anterior orbitotomy, Lateral orbitotomy, medial orbitotomy, and transcranial orbitotomy which will be discussed one by one. Calandriello et al. typically use a certain approach. The eye is retracted away from the CVM using a trans-conjunctival technique, which is routinely employed even for large lesions. Entering Via trans conjunctival opening securing EOM lesion is reached, sometimes to have a better field to locate intra-Conal lesions, extraocular muscles needed to cut at their insertion. Typically, the lesion is stitched with the first suture. To minimize the size of the lesion, manual pressure or a needle puncture might be used. A traction suture can help the mass slide anteriorly during cautious dissection. A cryoprobe can also be used to make the lesion easier to remove. A lateral canthotomy is required to better expose it. There are also descriptions of several transcutaneous incisions.

2) Lateral orbitotomy

In a retrospective analysis by Pedro Clarós et al., a series of 76 (94.7%) patients were evaluated, and the majority of surgeries were lateral orbitotomies. Most individuals who had proptosis before surgery improved when their VA was evaluated six months following surgery. VA improvement following surgery appeared to be influenced by the size of the tumour, preoperative VA, and aberrant funduscopy.

This tactic is favoured by many teams. Lateral orbitotomies provide an adequate view of tumors, with the possibility of multiple orbital incisions including a wide marginotomy of the deep sphenoid wing for

OCMV's extending to the apex. When a lateral orbitotomy exposes an OCMV that is close to the optic nerve, the need for bone resection should be determined by the posterior extension of the lesion. Precisely, the excision of an anterior small orbital cancer without an osteotomy will reduce morbidity.

3) Medial orbitotomy

Lesions occupying the medial aspect of the optic nerve.

4) Transcranial orbitotomy

More intrusive methods come with a high risk of serious consequences. Additionally, these surgical techniques are recommended for lesions that are in the back of the orbit, especially if they are lateral to or above the optic nerve. A frontal craniotomy is a highly invasive treatment, even in the hands of experienced surgeons, an intracranial trans-dural surgery thought to be associated with higher postoperative morbidity due to the manipulation and retraction of the brain and cranial nerves at the apex. Apical OCMV with severe vision loss and imaging evidence of superior and lateral juxta neuronal location suggesting strong connections with significant regions may finally be treated using a transcranial orbitotomy approach.

Conventional surgical approach for Lesions involving orbital apex

Surgery reveals the anterior portion of the OCMV when it outstretches to the orbital apex. A 4/0 slick suture passed through the body mass, allowing the lesion to deflate and be gently pulled out of place after excision. A watchful examination of preoperative imaging is advised to distinguish between lymphatic venous malformation and pure non-distensible CVM to prevent post-procedure bleeding, ischemia and nerve-related damage to the optic nerve.

Pros of invasive procedures

Dissecting the OCMVs markedly reduces symptoms and signs such as eye protrusion of the eyeball, Vision, visual field, dropping of the eyelid, and double vision, with fewer complications. Further, surgical removal allows histopathological diagnosis to make precise diagnoses among differentials.

Complications related to invasive procedures

The majority of complications are minor, and no serious complications related to lateral orbitotomy have been reported. With an overall complication rate of 23.7%, these included superior palpebral oedema, subconjunctival bleeding, chemosis, and lateral rectus damage. Mild problems are extremely common and typically go away on their own. Some teams have reported rare, severe consequences such as irreversible

visual loss right away following surgery, significant visual degradation caused by optic nerve damage, and lifelong visual loss from intra-orbital haemorrhage. Following surgical excision of OCMVs, VA worsening ranged substantially from 3% to 32%. Bleeding during and after surgery is not uncommon. In a study by Diego Strianese et al., the excision of OCMV situated in the posterior-lateral portion of the orbit involving the orbital apex resulted in isolated pupil changes/tonic pupil with deficient accommodation. In lateral orbitotomy approach and moving inferiorly through the lateral rectus, postoperative dropping of the eyelid is reported to range from 13% to 59% and postoperative diplopia occurs in about 20% of patients and is highly prevalent.

Non-Invasive Approaches

Comprises trans nasal endoscopic extraction, cryo extraction, sclerotherapy, and Gamma knife radiosurgery approaches to and via the orbit, via either trans nasal or trans palpebral pathways. The medial wall and orbital apex decompression method to the orbit, which was modified for trans-nasal endoscopic sinus surgery, is recommended for medial extra-conal lesions as well as for intra-conal lesions lying inferior and medial to the optic nerve. Although in some circumstances the superior window between the MRM and the SO muscle is favoured, the dissection corridor in intra-conal surgical procedures is typically between the MRM and IRM. The avoidance of complications related to an invasive approach is addressed by a less invasive endoscopic approach with decreased recovery time and better cosmetics.

1) Endoscopic trans-nasal orbital approach

For benign soft-tissue masses and OCMV located in the medial-inferior quadrant of the orbit, the intra-conal position, are ideal for trans-nasal management since they maintain their shape and can be easily manipulated without excessive risk of rupture

A) A four-handed bi-nostril includes a posterior septectomy which increases the likelihood of postoperative nasal crusting.

B) A bimanual single nostril method necessitates more extensive manipulation of nasal tissues and provides an adequate field to operate on the mass and its neighbouring structures.

Procedure

It is necessary to identify the recti muscles particularly medial and inferior after the periorbital window has been made. These muscles serve as the dissection corridor, not the muscle fibres that lead to the intra-conal cavity. When addressing the medial intra-conal space trans-nasally, the MRM must be moved because it serves as the primary marker of the medial orbit. Trans-septal sutures may be used in some situations to

medialize the medial rectus muscle. According to reports, a medialized and stiffened medial rectus muscle is simpler to handle and produces broader surgical fields. The MRM's neuronal and vascular branches, however, run the risk of being damaged by excessive or extended medialization. These originate from the oculomotor nerve and the ocular artery, respectively, and they travel in different directions before arriving at the MRM's lateral side. Pedicled naso septal flap is used for orbital reconstruction after removal of the orbital lesion via endo nasal approach to lessen the chance of postoperative diplopia and enophthalmos. In intra-conal orbital tumours, the minimally invasive 360-degree surgical technique with full endoscopic imaging can also be efficient and safe.

Contraindication to endoscopic approach

Endoscopic trans-nasal orbital surgery should still be regarded as a relative contraindication for non-contiguous lesions that reach super-laterally to the optic nerve and should be better handled by a superior or lateral orbitotomy.

Disadvantages associated with noninvasive endoscopic procedure

Endoscopic surgery to remove tumours from the orbital apex has become more common in recent years, but its main drawbacks are the inability to operate with two hands and the lack of binocular vision and three-dimensional vision.

2) Cryoextraction of orbital tumors

Putterman and Goldberg published the first description of cryoextraction of orbital malignancies in 1975. In two cases of intraorbital intra-conal hemangiomas that were excised via a trans-nasal technique; the Paolo Castelnovo et al study demonstrated outstanding safety results with the use of the cryoprobe. Hemangiomas were close to blood arteries and nerves and were enclosed. The temporary but effective contact between the probe's tip and the exposed surface of the neoformation is created by the Joule-Thompson effect. It enables the surgeon to gently traction the neoformation to break up adhesions with the surrounding tissues. Due to their success in the removal of fluid-filled intra-orbital lesions, cryoprobes serve as an auxiliary tool in the arsenal of orbital surgeons. Cryoprobes can be utilised in a transnasal-only procedure to remove intra-conal hemangiomas. Regarding this, the capability to medialize the neoformation and carry out removal progressively in the nasal fossa, outside the orbital space, aids in lowering the surgical time and injury related to intra-orbital lesion removal. To validate safety and efficacy, further instances must be examined.

3) Sclerotherapy

Patients who don't want to have surgery may benefit from the least invasive treatment option of sclerotherapy.

4) Gamma knife radiosurgery

In 96% of patients with apical lesions of the orbit, GKRS was found to be beneficial. With multiple sessions of GKRS, a considerable improvement in vision, visual field, RNFL thickness, proptosis, and diplopia, as well as a significant decrease in tumour volume. Patients with orbital apex lesions showed tumour reduction in anecdotal small case series treated with fractionated stereotactic radiotherapy without any noticeable side effects. After a round of fractionated stereotactic radiation, the authors stated that the tumour had shrunk by an average of 60% overall, preventing total blindness or additional vision loss with an improvement in the visual field. An alternate method of treating inaccessible and unresectable tumours is fractionated radiation. The mechanism of GKRS is known less, one hypothesis is that the radiation causes thrombosis and subsequent fibrosis within the lesion, which causes the vascular gaps to close and the lesion to contract. Radiation therapy may hasten the thrombotic and secondary fibrosis process in these lesions because venous stasis may make cavernous malformations more susceptible to thrombosis.

Pros of noninvasive surgical approach

The endo-nasal approach is usually preferred in types 1 and 2 in lesions medial to the optic nerve. It is a minimally invasive technique that avoids the need for skin incisions and significant bone resection. In addition, it provides a better view due to the use of magnified and stellar optics.

Complications related to the non-invasive approach

Nasal crusting and postoperative cerebrospinal fluid leak are complications related to a noninvasive approach. In low-flow vascular lesions, bleeding related to frontotemporal and parietal approach cerebrospinal fistulae or meningitis can be prevented by applying a traction suture.

A summary of the procedures and their pros and cons is provided in Table 2 for better understanding.

Techniques	Pros	Cons
Invasive		
Anterior orbitotomy	Marked reduction of eye protrusion, vision, visual field, dropping of eyelid, double vision, histopathological diagnosis to make precise diagnosis	superior palpebral oedema, subconjunctival bleeding, chemosis, and lateral rectus damage, intra and post-op bleeding, tonic pupil with deficient accommodation, post-op ptosis
Lateral orbitotomy		
Medial orbitotomy		
Transcranial orbitotomy		
Non Invasive		
Endoscopic trans-nasal orbital approach	Less need for skin incisions and significant bone resection, better view, less bleeding, rapid	Can end up in severe complications with a high learning curve, the expertise required
Cryoextraction		

Table 2: Summary of the Techniques and their pro and cons

Limitations of this study

Unavailability of data on complications related to noninvasive approaches, limited studies available on non-invasive approaches and less data available on extended follow-ups.

Conclusion

Both Invasive and noninvasive techniques have pros and cons related to surgery, while emerging noninvasive techniques are being adopted these days to lessen the collateral damage intraoperatively and rapid recovery postoperatively, nevertheless, the invasive approach has its own advantage, a high learning curve is required for a noninvasive approach which can be addressed by good and frequent practice. However, both approaches are surgeon and technique-dependent. In order to correctly determine the effects of the intervention on OCV, more trials with extended follow-ups are required.

References

- Calandriello L, Grimaldi G, Petrone G, Rigante M, Petroni S, Riso M, Savino G. Cavernous venous malformation (cavernous hemangioma) of the orbit: Current concepts and a review of the literature. *Surv Ophthalmol.* 2017 Jul-Aug;62(4):393-403. doi:10.1016/j.survophthal.2017.01.004. Epub 2017 Jan 26. PMID: 28131871.
- Lenzi, R., Bleier, B.S., Felisati, G. et al. Purely endoscopic trans-nasal management of orbital intraconal cavernous haemangiomas: a systematic review of the literature. *Eur Arch Otorhinolaryngol* 273, 2319–2322 (2016). <https://doi.org/10.1007/s00405-015-3733-3>
- Clarós P, Choffor-Nchinda E, Lopez-Fortuny M, Claros A, Quintana S. Orbital cavernous haemangioma; profile and outcome of 76 patients managed surgically. *Acta Otolaryngol.* 2019 Aug;139(8):720-725. doi:

10.1080/00016489.2019.1618913. Epub 2019 Jun 1. PMID: 31155992.

4) Castelnovo P. et al. Endoscopic Transnasal Cryo-Assisted Removal of Orbital Cavernous Hemangiomas: Case Report and Technical Hints, *World Neurosurgery*, 2019, 126, 66-71, <https://doi.org/10.1016/j.wneu.2019.01.235>.

5) Strianese D, Bonavolontà G, Iuliano A, Mariniello G, Elefante A, Liuzzi R. Risks and Benefits of Surgical Excision of Orbital Cavernous Venous Malformations (So-Called Cavernous Hemangioma): Factors Influencing the Outcome. *Ophthalmic Plast Reconstr Surg.* 2021 May-Jun 01;37(3):248-254. doi: 10.1097/IOP.0000000000001767. PMID: 32826827.

6) Young SM, Kim KH, Kim YD, Lang SS, Park JW, Woo KI, Lee JI. Orbital apex venous cavernous malformation with optic neuropathy: treatment with multisection gamma knife radiosurgery. *Br J Ophthalmol.* 2019 Oct;103(10):1453-1459. doi: 10.1136/bjophthalmol-2018-312893. Epub 2019 Jan 5. PMID: 30612095.

7) Lee WJ, Cho KR, Choi JW. Stereotactic radiosurgery for orbital cavernous venous malformation: a single centre's experience for 15 years. *Acta Neurochir (Wien).* 2021 Feb;163(2):357-364. doi: 10.1007/s00701-020-04575-4. Epub 2020 Sep 15. PMID: 32929542.

8) Meng X, Feng X, Wan J. Endoscopic Endonasal Transsphenoidal Approach for the Removal of Optochiasmatic Cavernoma: Case Report and Literature Review. *World Neurosurg.* 2017 Oct;106:1053.e11-1053.e14. doi: 10.1016/j.wneu.2017.07.026. Epub 2017 Jul 13. PMID: 28712905.

9) Kim M, Gudis DA, Tooley AA, Kazim M. Trans-septal suture retraction for endoscopic orbital surgery. *Orbit.* 2020 Oct;39(5):336-341. doi: 10.1080/01676830.2019.1692040. Epub 2019 Nov 18. PMID: 31739703.

10) Caballero-García J. et al. Minimally Invasive 360-Degree Approach to Intraconal Orbital Tumors, *American Journal of Ophthalmology*, 2021, 224, 301-309, <https://doi.org/10.1016/j.ajo.2020.07.035>.

11) PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

Affiliated with California University