

Trigemino-cardiac Reflex after Direct Infusion of Chemotherapy into the Ophthalmic Artery for Retinoblastoma

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Abstract

Introduction: Direct intra-ophthalmic artery infusion of chemotherapy has emerged as a front-line treatment modality for both early and advanced forms of retinoblastoma. The procedure has become common practice for neurointerventionalists at institutions with major ophthalmology centers. We present a case series of patients who manifest an autonomic reaction of acute hypoxemia, hypocapnia, hypotension, and bronchospasm consistent with trigemino-cardiac reflex. We report our experience with this reaction, which is commonly seen during pediatric strabismus surgery but until now, rarely seen in the neuroangiography suite.

Methods: We retrospectively reviewed our 5-year experience with intra-ophthalmic artery chemotherapy infusion for retinoblastoma. Procedure notes, anesthetic records, patient characteristics, and chemotherapeutic agents used were reviewed.

Results: Over a 5-year period, 199 treatment sessions were performed in 49 patients. Twenty-eight TCR events were observed in 18 patients. Twenty-seven of these were quickly terminated following interruption of chemotherapy infusion, ventilatory support, and administration of pressor agents. In one case the procedure was aborted due to the prolonged duration of the reflex. There were no permanent sequelae.

Conclusions: We found an appreciable incidence of trigemino-cardiac reflex to intra-ophthalmic artery infusion of chemotherapy in patients with retinoblastoma. Both interventionalists and anesthesiologists should be aware of this potential event and be prepared to provide immediate resuscitative measures.

Introduction

Recent interest in super-selective intra-ophthalmic artery chemotherapy infusion for retinoblastoma has created a rise in the volume of pediatric interventions for neuro-interventionalists and anesthesiologists at institutions with major ophthalmology centers. Due to the age of the patients, as well as the need for complete immobility, these cases are typically performed under general anesthesia. In our 5-year experience with this procedure we have observed many episodes characterized by hypoxemia, hypocarbia, hypotension, and evidence of bronchospasm. Other groups performing this procedure have briefly mentioned such autonomic events, but detailed reports are lacking [1-3]. This reflex has traditionally been known as the oculocardiac reflex (OCR), but more precise neuro-anatomic targeting has led many to adopt the more physiologic term trigemino-cardiac reflex (TCR). This report of our experience with the TCR is intended to highlight the growing relevance of this phenomenon.

Case Report

Patients and methods

The Institutional Review Board of the University of Miami/Miller School of Medicine approved the retrospective chart review study of

patients who received intra-arterial ophthalmic chemotherapy at our center. At the time of the procedure, all patients were consented by their guardians (as per institutional protocol) to allow the release of medical information for the purpose of research, after the removal of identifying data. Our anesthesiology database was reviewed to identify patients who received general anesthesia for intra-arterial chemotherapy for the treatment of retinoblastoma between January 2008 and December 2012. Over this time period, 199 cases were performed on 49 different patients whose ages ranged from 14 months to seven years old. These anesthetic records were reviewed after the patients' names and other identifying data were removed. For the purpose of this study, a positive TCR response was defined as two or more of the following criteria occurring upon catheter insertion into or advancement through the ophthalmic artery, or during intra-arterial infusion of contrast, flush, or chemotherapeutic agent:

- A drop in the systolic, diastolic, and/or mean blood pressure of 20% or greater,
- A decrease in heart rate by 20% or greater,
- A drop in the pulse oximeter reading of 20% or greater,
- A decrease in the end-tidal carbon dioxide of 20% or greater,
- An increase in the peak inspiratory pressure of 20% or greater.

Anesthesia technique

All patients were evaluated and examined in our anesthesiology clinic prior to the procedure. Due to the neurointerventionalists' exclusion criteria, patients with pre-existing cardiopulmonary conditions were not candidates for this therapy and were therefore excluded from the study. All children arrived to the neuroradiology suite with either an intravenous line placed previously or a port that had been accessed prior to their arrival. All children were medicated with midazolam 0.15 mg/kg IV prior to the application of standard monitors. After preoxygenation, general anesthesia was induced with fentanyl 2 mcg/kg, glycopyrrolate 4 mcg/kg (up to a maximum dose of 200 mcg), propofol 2 mg/kg and rocuronium 1 mg/kg. Each patient was maintained on an O₂/air mixture (FIO₂ 30-40%) with sevoflurane (2%). Due to the non-stimulating nature of the procedure, additional narcotic was not used. Rocuronium was titrated in increments of 0.25 mg/kg to maintain no more than one twitch on a train-of-four monitor. At the conclusion of the procedure, neostigmine 0.7 mg/kg was given with an equal volume of glycopyrrolate (0.2 mg/cc). When adequate spontaneous ventilation had resumed (tidal volumes at least 5 ml/kg) the endotracheal tube was removed and the sevoflurane was discontinued. The purpose of performing a deep extubation was to minimize bucking, thereby lessening the possibility of reopening the femoral puncture site. Midazolam was given in 0.5 mg doses if emergence resulted in significant patient movement.

Endovascular technique

A single wall micropuncture technique was used to cannulate the femoral artery and place a 4F vascular sheath. Heparin was infused intravenously to maintain adequate anticoagulation, as measured by an ACT between 250-300 seconds. The vascular sheath and diagnostic catheter were perfused with heparinized saline flush throughout the procedure. A 4F angled Terumo catheter was advanced over a 0.035 inch Terumo guidewire and advanced over the aortic arch into the carotid artery of the tumor side. A Marathon microcatheter was maneuvered over a Mirage guidewire into the ophthalmic artery and an angiogram was performed. Melphalan, prepared in 10 ml iodinated contrast and 20 ml of sterile saline, was dosed according to patient size and infused over 30 minutes. In lieu of melphalan, two of the patients received topotecan and one received carboplatin at the discretion of the ophthalmologist. Chemotherapy was delivered by manual pulse injection. Roadmaps were performed at 3-4 minute intervals to confirm anterograde flow through the ophthalmic artery during infusion. A follow-up angiographic run was performed after infusion and the microcatheter was removed, a final internal carotid angiogram was performed before removing the diagnostic catheter. The vascular sheath was removed and hemostasis was achieved by manual compression.

Results

18 of the 49 patients showed evidence of TCR; a total of 28 events were identified from a series of 199 sessions of ophthalmic artery chemotherapy infusion. The reflex occurred during selective angiography of the ophthalmic artery in 21 cases, and upon flushing of or infusion through the catheter in the remaining 7 cases. No incidences of the reflex were noted during the catheter excursion through the internal carotid artery or cavernous sinus; TCR was triggered only in response to the microcatheter entry into the ophthalmic artery itself. Recognition of the TCR was made according to the following distribution of inclusion criteria:

- Decrease in SBP 20% or greater: 18 cases (64.3%). Average drop in SBP among all cases: 26.4%.
- Decrease in DBP 20% or greater: 14 cases (50%). Average drop in DBP among all cases: 20.4%.
- Decrease in MBP 20% or greater: 16 cases (57.1%). Average drop in MBP among all cases: 25.1%.
- Decrease in HR 20% or greater: 2 cases (7.1%). Average drop in HR among all cases: 0.2%.
- Decrease in SpO₂ 20% or greater: 11 cases (39.3%). Average drop in SpO₂ among all cases: 21.6%.
- Decrease in ETCO₂ 20% or greater: 21 cases (75%). Average drop in ETCO₂ among all cases: 37.4%.
- Increase in PIP 20% or greater: 24 cases (85.7%). Average rise in PIP among all cases: 83.3%.

One of the episodes of TCR was prolonged (lasting greater than 3 minutes) and the procedure was aborted; in all other cases it was transient enough to resume after vital sign stabilization. 7 patients received a single dose of intravenous phenylephrine (1 mcg/kg) to support blood pressure, and 2 patients received a single dose of intravenous epinephrine (1 mcg/kg) to support blood pressure and provide bronchodilation. No permanent deficits occurred.

Discussion

The trigemino-cardiac reflex was first described in a cat and rabbit model by Kratschmer in 1870 as a response to inhaled irritants [4]. This event has also been referred to as the trigemino-cardiac, oculocardiac, oculo-respiratory, trigemino-valgus, and oculo-vagal reflex [5-8]. In the 1950s, reports of TCR in pediatric strabismus surgery documented early clinical observations of the reflex while surgeons applied traction on the extraocular muscles [9]. In those cases, halting the stimulating maneuver generally aborted the reflex. Atropine and removal of nasal packing were anecdotally successful in terminating a TCR during rhinoplasty [10]. While the bulk of TCR has been described in relation to pediatric strabismus surgery [5,11], it has also been documented during endoscopic sinus, craniofacial, and skull base surgeries [12-16]. In 1999, Schaller et al. were the first to describe the TCR during a neurosurgical procedure. Their series of cerebellopontine angle tumor operations had an 11% incidence of TCR upon manipulation of the trigeminal nerve near the brainstem [17]. More recently, severe TCR leading to asystole during transsphenoidal surgery of the pituitary has also been reported [7,18].

As endovascular treatment of neurological disease has advanced in recent decades, more numerous reports of TCR have followed. TCR during endovascular embolizations has been documented after flushing a microcatheter in the internal maxillary artery during treatment of three juvenile nasopharyngeal angiofibromas and a dural arteriovenous fistula [19-21]. The injection of DMSO before Onyx is a common feature in these cases. Some of our cases also occurred during flushing of the microcatheter, however neither DMSO nor Onyx was used. Iodinated contrast is widely used without this effect, thus we doubt that the content of the flush is to blame.

Lang et al. proposed a plausible mechanism to explain the TCR [12]. He speculated that sensory afferents of the trigeminal nerve, in this case innervating the ophthalmic artery, have synaptic connections between the main trigeminal sensory nucleus and the motor nucleus of the vagus nerve. Trigeminal stimulation via manipulation of the orbit, facial sinuses, dura, or nerve itself can trigger profound sinus bradycardia, hypotension, apnea, and bronchospasm. Our hypothesis

is that the trigeminal afferents, particularly in these young patients, act as exquisitely sensitive baroreceptors to the increased pressure during microcatheter insertion and infusion. Connections between afferent trigeminal nerve signals and vagal efferent nerves appear to be the source of this autonomic response to ophthalmic artery infusion.

Other centers have also reported an increased volume of super-selective intra-arterial chemotherapy and have likewise noted bronchospasm followed by bradycardia; these cases are often managed by cessation of catheter manipulation and administration of epinephrine in cases of hypotension [1]. The groups known to us to have the largest experiences with intra-arterial infusion of chemotherapy for retinoblastoma noted an almost universal pairing of bradycardia with the reflex, the former group considering it a surrogate for successful infusion into the ophthalmic artery [3,22]. Bradycardia was uncommon in our cohort, occurring on only 7.1% of the cases. There is no evidence that they premedicated their patients with an anticholinergic agent; our use of glycopyrrolate at induction may have been the reason we did not see a significant incidence of bradycardia with the reflex. Others authors have also noted an absence of bradycardia, and in fact have documented tachycardia being present at the initiation of the TCR [23].

Evidence for effective pre-medication is lacking. The clinical settings in which TCR is observed involve heterogeneous anatomy and patient characteristics. Stopping the provocative manipulation is a simple and in our experience, usually effective method of aborting a TCR. Clinical evidence has suggested that hypercapnia in children promotes the reflex and should be avoided [24]. Whether pre-administration of vagolytics or sympathomimetics is safe and effective is unproven in this population. It has been suggested but not tested whether the intravenous administration of atropine or glycopyrrolate could prevent TCR [25]; this was not supported by our data. Alternative catheterization techniques (e.g. balloon assisted) may result in a differing incidence of TCR; these techniques were not practiced by our neurointerventional team, but this possibility requires further investigation.

Conclusion

To the best of our knowledge, this is the largest case-series to report the trigemino-cardiac reflex during an endovascular procedure. Endovascular procedures are rapidly growing in terms of techniques used and diseases treated. Thoughtful communication with the entire medical team can facilitate the identification and treatment of unexpected effects to procedures, particularly during the early adoption of new techniques. Neurointerventionalists and anesthesiologists must be aware of the TCR and ready to provide supportive therapy.

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