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Clinical Study

Potential neurotoxic effects of polymethylmethacrylate during cranioplasty

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ABSTRACT

Cranioplasty for the surgical correction of cranial defects is often performed using polymethyl methacrylate (PMMA), or bone cement. Immediately prior to PMMA application, a liquid monomer form (methylacrylate) and a benzoyl peroxide accelerator are mixed resulting in polymerization, an exothermic reaction during which monomer linking and subsequent formation of solid polymer occur. The potential side effects of residual methylacrylate monomer toxicity and thermal damage of neural tissue during PMMA hardening have been described in various *in vitro*, animal, and cadaveric studies; however, clinically documented *in vivo* neurotoxicity in humans attributed to either of the above two mechanisms during PMMA cranioplasty is lacking. We present a series of four patients operated for removal of cerebellopontine angle lesions and two operated for the excision of parieto-occipital tumors who sustained cranial neuropathies and encephalopathies with transient or permanent neurological deficits that could not be attributed to surgical manipulation. We hypothesize that these complications most likely occurred due to thermal damage and/or chemical toxicity from exposure to PMMA during cranioplasty. Our case series indicates that even small volumes of PMMA used for cranioplasty may cause severe side effects related to thermal damage or to exposure of neural tissue to methylacrylate monomer.

1. Introduction

Cranioplasty refers to the surgical correction of craniofacial defects, such as those occurring following cranial tumor excision, infection of craniotomy bone flaps, neurotrauma surgery, surgical decompression to control malignant intracranial hypertension, and congenital or acquired craniofacial disorders. In reconstructing the defect, a variety of materials are currently used, including autologous bone as well as allogenic and alloplastic materials.

In the absence of autologous bone graft, polymethyl methacrylate (PMMA), or bone cement, is one of the most frequently used alloplastic materials for cranioplasty [1]. PMMA is supplied by the manufacturer as a powder polymer with a liquid monomer form (methylacrylate) together with benzoyl peroxide accelerator. Mixing of the two components results in polymerization, an exothermic reaction during which monomer linking and subsequent formation of solid polymer occur. Heat-induced tissue damage may occur during polymerization [2,3]. Moreover, methyl methacrylate monomer is a highly cytotoxic, strong lipid solvent [4–6], and saline irrigation of the PMMA prosthesis during cranioplasty could potentially expose neural tissue to residual methylacrylate monomer with subsequent neuronal damage.

The possibility of heat-induced nerve damage has been described in the literature during PMMA vertebral augmentation [4] and allergic reactions related to cranioplasty have also been reported [7,8]. However, to the best of our knowledge, other than *in vitro*, animal, and cadaveric studies, there are no reports in the English literature describing the possibility of heat or chemical-induced neural damage directly related to the use of PMMA during cranioplasty in living patients.

We report a series of six patients who underwent craniectomy and PMMA cranioplasty for the resection of brain tumors. In these patients, there was no cortical or cranial nerve damage during tumor resection, but they developed symptoms and signs of neuronal dysfunction either during cranioplasty or while awakening. We suggest that their symptoms may be attributable to methylacrylate monomer neurotoxicity sustained during saline irrigation of the prostheses and/or to thermal injury. To our knowledge this is the first report of *in vivo* neurotoxicity related to PMMA exposure during cranioplasty.

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Table 1
Patient demographic data, tumor location, complications, and outcomes

Patient	Age/ Sex	Tumor type, location	Cranioplasty complication	Outcome
1	16/M	Right CPA epidermoid	Disappearance of BAER waves III, V; delayed awakening, confusion, and restlessness	Complete recovery
2	28/M	Left CPA meningioma	Delayed awakening, confusion, and restlessness	Complete recovery
3	40/F	Left CPA meningioma	Delayed awakening, confusion, and restlessness; transient CN III/VI palsy	Complete recovery
4	50/M	Right acoustic neuroma	Delayed awakening, confusion, and restlessness requiring overnight intubation; transient left CN III palsy	Complete recovery
5	41/F	Left occipital Langerhans cell histiocytosis	Hemianopia	Partial recovery
6	66/F	Right intra-osseous meningioma, parasagittal sensory area	Left dorsal foot numbness	Partial recovery

BAER = brainstem auditory evoked response, CN = cranial nerve, CPA = cerebellopontine angle, F = female, M = male.

2. Materials and methods

2.1. Cranioplasty procedure

In our Medical Center, skull defects occurring due to craniectomy have been repaired with a cranioplasty procedure performed during closure. In cases where a PMMA prosthesis is used, the implant is made by mixing the copolymer powder with methyl methacrylate liquid monomer at a ratio of approximately 2:1. After the mixture reaches a stiff moldable consistency, the prosthesis has been molded *in situ* during cranioplasty in order to achieve better cosmetic results. To prevent thermal injury to the dura and neural tissue during polymerization, a carefully arranged interface of moist Gelfoam (Pfizer, New York, NY, USA) has been placed between the PMMA and the underlying dura or dural substitutes, and the implant has been continuously irrigated with cold saline during PMMA hardening. With these precautionary steps, we have assumed that we ensured no direct contact between the PMMA implant and brain tissue at any time during cranioplasty procedures.

2.2. Case report documenting neurotoxicity during cranioplasty

A 16-year-old boy (Table 1, patient 1) who presented with right trigeminal neuralgia underwent craniectomy for a right cerebellopontine angle (CPA) epidermoid cyst (Fig. 1). The patient's past medical history, physical examination, and routine preoperative work-up were unremarkable.

The patient was operated on his left side in a 3/4 prone position via right retrosigmoid approach with full neuromonitoring, including brainstem auditory evoked response (BAER) monitoring. The craniectomy was performed and the tumor was completely removed in an uneventful surgery.

Baseline BAER, performed prior to skin incision, appeared normal, and throughout the surgery and dural closure all auditory brain response (ABR) waves were detected with only typical minor fluctuations in comparison to the baseline study. Following tumor removal, PMMA cranioplasty began on a carefully placed supportive layer of gauze pads, Gelfoam, and dural substitute. Then, during PMMA hardening, there was a sudden, unexpected disappearance of the right cochlear nerve BAER readings (right ABR, waves III and IV–V, Fig. 2).

The patient recovered from anesthesia relatively slowly and with initial confusion and restlessness, but without any focal neurologic deficit. He had an uncomplicated postoperative course and was discharged from the hospital free of trigeminal neuralgia. On clinical follow-up he was symptom free, denying any episodes of neuralgia, and he reported no hearing disturbance. On follow-up MRI (Fig. 3) complete tumor removal was noted. Follow-up audiometry examination showed normal bilateral hearing.

Based on the smooth course of the surgery and anesthetic management, we attributed the surprising disappearance of BAER readings during cranioplasty to transient chemically-induced neuropathy caused by exposure to residual methacrylate monomer that occurred during irrigation of the PMMA prosthesis.

2.3. Additional reports of PMMA-related neurotoxicity

Following this surprising development, we retrospectively reviewed our surgical notes to determine whether other patients had possibly experienced some form of neurological toxicity related to PMMA cranioplasty. We identified five additional patients operated on during a 2 year interval for the removal of brain tumors who had experienced remarkably similar difficulty emerging from anesthesia, demonstrating a slow waking-up process with initial restlessness and confusion or drowsiness, or developed focal signs and symptoms of central nervous system dysfunction that could not be explained by direct surgical manipulation during tumor removal.

The medical records of all six patients were retrospectively reviewed. Demographic data, details relating to the cranioplasty procedure, pre- and postoperative laboratory and imaging investigations, surgical notes, intraoperative neuromonitoring reports, and follow-up data were retrospectively reviewed.

3. Results

3.1. Patients

The six patients included three males and three females, mean age 40 years (range 16 to 66). Surgery was performed for resection of CPA meningiomas in two patients, for a removal of a CPA epidermoid cyst (described above) in one, and excision of an acoustic neuroma in one. These four patients were operated via retrosigmoid approach. Two patients underwent surgical excision of tumors involving the skull in the parieto-occipital area; one for an intraosseous meningioma and one for Langerhans cell histiocytosis of the skull that involved the dura. Craniectomy was performed because of extreme pneumatization in two patients, pneumatization and difficult emissarial venous anatomy in two, and tumor-skull involvement in two patients (Table 1).

Prior to surgery, all patients underwent routine laboratory and imaging investigation. They were all clinically stable and free of infection. All surgeries were performed by the same senior neurosurgeon (S.S.). PMMA cranioplasty was performed following uncomplicated tumor excision and hemostasis. In all six reported