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Review

A systematic review of cranioplasty material toxicity in human subjects

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ABSTRACT

Purpose: Local and systemic toxic reactions to implanted materials can result in morbidities. However, little is reported about cranioplasty implants. Therefore, we performed a systematic review on the toxicity of different materials used for cranioplasty implants.

Materials and methods: A systematic search was conducted by browsing the Pubmed, Embase, and Cochrane Library databases. All human studies that identified toxic (aseptic) reactions to any types of material used as cranioplasty implants or onplants, published up to January 1, 2019, were included in the review.

Results: Nineteen studies were identified. Collectively, 36 patients endured some type of toxic reaction to an implanted material. Eleven studies presented several types of toxicity for PMMA cranioplasties in several tissue types. One article highlighted the risk of neurotoxicity for PMMA cranioplasty. Three articles presented toxic reactions to calcium phosphate and titanium implants. Three additional articles presented toxic reactions to PEEK, polypropylene-polyester, and polyethylene.

Conclusion: All materials currently used for cranioplasty showed occasional toxicity and morbidities. Therefore, none can be considered completely biologically inert. We found that aseptic inflammatory reactions have been underreported in the literature due to a high incidence of infections with questionable evidence.

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1. Introduction

Reconstruction of postcraniectomy skull defects prevents and treats early-stage symptoms of the 'syndrome of the trephined', characterized by motor function decline (Ashayeri et al., 2016). Cranioplasty also improves late-stage aesthetic blemishes associated with this syndrome as well as quality of life (Lindner et al., 2017).

Despite its status as the gold-standard treatment, cranioplasty with autologous bone grafts leads to graft resorption in 11.2–50% of cases (Bowers et al., 2013; Van de Vijfeijken et al., 2018), with the resulting defects requiring replacement by an alloplastic material (Zanotti et al., 2016). Implanted alloplastic materials can cause an acute inflammatory reaction followed by a chronic inflammatory reaction (CIR). If the CIR does not attenuate, a foreign-body reaction (FBR) can ultimately occur, which is characterized by monocytes, macrophages, foreign-body giant cells, and tissue granulation at the biomaterial interface (Anderson et al., 2008; Sheikh et al., 2015). Additionally, due to the proximity of the cranioplasty to the brain, material neurotoxicity should be considered. The toxicity (FBR, aseptic CIR, allergic reaction, or neurotoxicity) caused by one of these materials could lead to explantation and damaged soft tissue debridement, making the reconstruction exponentially more challenging and negatively impacting patient welfare. To ensure the safety of patients, these materials need to be biocompatible (both locally and systemically), biologically inert, and nontoxic if degraded (Zanotti et al., 2016).

Currently, polymethylmethacrylate (PMMA), calcium phosphate (CaP), polyether ether ketone (PEEK), and titanium alloys are the most commonly used materials. However, little is reported on their complication rates in terms of local and systemic toxicity. Although PMMA is the most popular material for cranioplasty implants (Van de Vijfeijken et al., 2018), in vitro studies have demonstrated cytotoxic effects for residual monomers produced during

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incomplete polymerization of PMMA (Goiato et al., 2015). Animal studies have reported CaP migration into the dura following resorption deficiency, generating local inflammatory reactions followed by FBR (Moreira-Gonzalez et al., 2005). Furthermore, allergic reactions to commercially pure titanium or titanium alloys (Ti_6Al_4V) have been observed (Goutam et al., 2014), along with delayed-type hypersensitivity reactions to PEEK (Maldonado-Naranjo et al., 2015). However, little is known about in vivo human subject toxicity morbidities.

To gain further knowledge of the biological effects of cranioplasty biomaterials, we conducted a systematic review with the following null hypothesis: 'There is no difference in the incidence of material-derived toxicity across currently reported materials used for cranioplasty implants in human subjects'.

2. Material and methods

A systematic search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines was performed on the toxicity of materials used for cranioplasty implants. The following search engines were used: PubMed, Embase, Web of Science, and Cochrane Database.

The Patient–Intervention–Comparison–Outcome (PICO) process was used to organize our search strategy. Because all biomaterials used for cranioplasty implants needed to be included, the comparison field was omitted, resulting in a PIO search strategy. The keywords presented in Table 1 were used to design our search strings. Keywords were adapted depending on which search engine was employed. For instance, this gave the PubMed search string shown in Table 2.

The inclusion and exclusion criteria are listed in Table 3. Articles in English, Dutch, German, French, Italian, and Hungarian were included. Articles published up to January 1, 2019 were reviewed.

At first, abstract selection was performed independently by all three authors. In cases where one article was selected by any author, the full text was assessed for eligibility. The final inclusion was decided unanimously by all authors.

Quality assessment was performed independently by the authors DEL and MYM. Because all included articles were case series, quality assessment was performed using the modified Delphi technique. A total of 20 questions were divided into seven categories: study objective, study population, intervention and cointervention, outcome measure, statistical analysis, results and conclusions, and competing interests and sources of support. Each question was answered with 'Yes', 'No', or 'Unclear'. Quality assessment for each article was appraised as follows: high risk of bias, 0–8 yes answers; moderate risk of bias, 9–15 yes answers; and low risk of bias, 16–20 yes answers.

When articles were found to be eligible, the authors DEL and DV independently extracted the following data: author(s); year of publication; number of patients and cranioplasty implants in the series; number of patients and cranioplasty implants with material-related toxicity of the implant; gender distribution; mean age of patients in years; indication for craniectomy; location of craniectomy; sinus involvement; time interval between craniectomy and cranioplasty; material used for cranioplasty fabrication; inlay or onlay; PMMA fabrication technique (direct or indirect); cement or ceramic CaP cranioplasty; type of cement CaP cranioplasty; type of titanium used; pre- or postoperative radiotherapy; primary or secondary cranioplasty; primary cranioplasty material; type of toxicity endured; examination of toxicity; and treatment of toxicity.

Due to the homogeneity across all studies, meta-analysis could not be performed.

3. Results

3.1. Study selection

A total of 457 articles were identified after systematically searching the literature (Fig. 1). Of the 214 articles retained after abstract screening, 18 were included in the systematic review. Argumentation for full-text exclusion is shown in Fig. 1. Full-text examination provided an additional eligible article. This resulted in a total of 19 articles included in the systematic review.

3.2. Study characteristics

Of the 19 studies, 11 (58%) were retrospective case series, and seven were case reports, of which two were post-mortem case reports. Only one study was a prospective case series (Table 4a). The studies were published between 1977 and 2018. Combining all studies, 1144 cranioplasty implants were performed on 1141 patients. Of these, a total of 36 patients (37 cranioplasty implants) endured a form of material-based toxicity (Table 4a).

Ten studies (53%) identified cranioplasty implant toxicity from acrylic, polymer, or PMMA only, or in combination with other materials. Toxicity to titanium and CaP variants were each acknowledged in three studies (16%). In only one study did a PEEK cranioplasty cause toxicity. Polypropylene-polyester knit (CODUBIX, Tricomed, Łódź, Poland) and polyethylene combined with titanium mesh (MEDPOR TITAN, Stryker, Kalamazoo, Michigan, United States) cranioplasties were also identified as toxic in one study each (Table 4a).

3.3. Cranioplasty material-based toxicity

3.3.1. Acrylic, polymer, and PMMA

After grouping all subjects in the 10 studies in question (Tysvaer and Hovind, 1977; Yoshii et al., 2001; Meel, 2004; Wurm et al., 2004; Brett-Major et al., 2008; Gautschi et al., 2010; Pikis et al.,

Table 1
Keywords used for search strategy.

Category	Keywords
Patient	Cranioplasty
Intervention	*Polymers:*
	Polymers, Monomer, Copolymer, Methacrylates, Polymethylmethacrylate, Bisphenol A-glycidyl methacrylate, Resin, Acrylic, Composite, Celluloid, Polycarpolactone, Poly(lactic acid), Poly(glycolic acid) Polyether ether ketone, Bone Cement, and Polyethylene
	Metals:
	Titanium, Alloy, Platinum, Aluminium, Lead, Platinum, Gold, Silver, Chrome, Cobalt, Molybdenum, Steel, and Iron
	Calcium phosphate:
	Ceramics, Calcium phosphate, Calcium phosphate derivatives, Alumina, Hydroxyapatite, Bioglass, and Silica
	Others:
	Biocompatible materials, Biomaterials, Biomimetic materials, and Alloplastic
Outcome	Toxicity, Inflammation, Foreign-body (Reaction), Hypersensitivity, Allergy, Neurotoxicity, Encephalitis, Meningitis, and Gliosis

Table 2
PubMed searchstring

Patient	("Cranioplasty"[tiab])
Intervention	(("Methacrylates"[Mesh] OR "Methacrylates"[tiab] OR methacrylat*[tiab] OR "Polymethyl Methacrylate"[Mesh] OR "Polymethyl Methacrylate"[tiab] OR Polymethyl Methacrylat*[tiab] OR "Polymethylmethacrylate"[tiab] OR "Bisphenol A-Glycidyl Methacrylate"[Mesh] OR "Bisphenol A-Glycidyl Methacrylate"[tiab] OR "Methylmethacrylate"[Mesh] OR "Bisphenol A"[tiab] OR "Bisphenol"[tiab] OR "Methylmethacrylate"[tiab] OR Methylmethacrylat*[tiab] OR "PMMA"[tiab] OR "Polymers"[Mesh] OR "Polymers"[tiab] OR polymer*[tiab] OR Monomer*[tiab] OR "Acrylic Resins"[Mesh] OR "Acrylic Resins"[tiab] OR "Resin Cements"[Mesh] OR "Resin Cements"[tiab] OR Resin* [tiab] OR acrylic* [tiab] OR "Composite Resins"[Mesh] OR "Composite Resins"[tiab] OR "Composite Tissue Allografts"[Mesh] OR "Composite Tissue Allografts"[tiab] OR composite* [tiab] OR biocomposite*[tiab] OR "celluloid" [tiab] OR "copolymer"[tiab] OR "poly(ethylene glycol)"[tiab] OR "PEG"[tiab] OR "Poly(lactide-co-glycolide)"[tiab] OR "PLGA"[tiab] OR "poly(lactide)"[tiab] OR "poly(lactic acid)"[tiab] OR "PLA"[tiab] OR "poly(glycolide)"[tiab] OR "poly(glycolic acid)"[tiab] OR "PGA"[tiab] OR "polycaprolactone"[tiab] OR "polycaprolactone"[Supplementary Concept] OR "polyfumarates"[tiab] OR "polyanhydride"[tiab]) OR ("polyetheretherketone"[Supplementary Concept] OR "polyetheretherketone"[tiab] OR "PEEK"[tiab] OR "Polyethylene"[Mesh] OR "Polyethylene"[tiab] OR "Polyethylenes"[Mesh] OR "Polyethylenes"[tiab]) OR ("Titanium"[Mesh] OR "Titanium"[tiab] OR titanium*[tiab] OR "titanium alloy (TiAl6V4)" [Supplementary Concept] OR "titanium alloy (TiAl6V4)" [tiab] OR "hydroxyapatite-titanium alloy" [Supplementary Concept] OR "hydroxyapatite-titanium alloy" [tiab] OR "Tantalum"[Mesh] OR "Tantalum"[tiab] OR "tantalum oxide" [Supplementary Concept] OR "tantalum oxide" [tiab] OR "Metals"[Mesh] OR "Metals"[tiab] OR "Metal Ceramic Alloys"[Mesh] OR "Metal Ceramic Alloys"[tiab] OR "Aluminum"[Mesh] OR "Aluminum"[tiab] OR "Lead"[Mesh] OR "Platinum"[Mesh] OR "Platinum"[tiab] OR "Gold"[Mesh] OR "Gold"[tiab] OR "Silver"[Mesh] OR "Silver"[tiab] OR "Chrome"[tiab] OR "Cobalt"[tiab] OR "molybdenum"[tiab] OR "Molybdenum"[Mesh] OR "steel"[tiab] OR "Steel"[Mesh] OR "Iron"[Mesh] OR "Iron"[tiab])) OR ("Bone Cements"[Mesh] OR "Bone Cements"[tiab] OR "Ceramics"[Mesh] OR "Ceramics"[tiab] OR "calcium phosphate" [Supplementary Concept] OR "calcium phosphate" [tiab] OR "Alumina"[tiab] OR "Hydroxyapatites"[Mesh] OR "Hydroxyapatite"[tiab] OR "Hydroxy-apatites"[tiab] OR "amorphous calcium phosphate" [Supplementary Concept] OR "amorphous calcium phosphate" [tiab] OR "Monocalcium phosphate monohydrate"[tiab] OR "MCPM"[tiab] OR Dicalcium phosphate*[tiab] OR "DCPA"[tiab] OR Dicalcium phosphate anhydr*[tiab] OR "calcium phosphate, dibasic, anhydrous" [Supplementary Concept] OR "dicalcium phosphate dihydrate"[tiab] OR "brushite "[tiab] OR "calcium phosphate, dibasic, dihydrate" [Supplementary Concept] OR "DCPD"[tiab] OR "Octocalcium phosphate"[tiab] OR "OCP"[tiab] OR "Precipitated hydroxyapatite"[tiab] OR "PHA"[tiab] OR "Monocalcium phosphate"[tiab] OR "MCP"[tiab] OR "calcium phosphate, monobasic" [Supplementary Concept] OR "alpha-Tricalcium phosphate"[tiab] OR ″α-Tricalcium phosphate"[tiab] OR ″α-TCP"[tiab] OR "beta-Tricalcium phosphate"[tiab] OR ″β-Tricalcium phosphate"[tiab] OR ″β-TCP"[tiab] OR "Tetracalcium phosphate"[tiab] OR "TetCP"[tiab] OR "biphasic calcium phosphates"[tiab] OR "BCP"[tiab] OR "Bioglass" [Supplementary Concept] OR "Bioglass" [tiab] OR "Bioactive glass" [tiab] OR "Silicon Dioxide"[Mesh] OR "Silicon Dioxide"[tiab] OR "Silica"[tiab])) OR ("Biocompatible Materials"[Mesh] OR "Biocompatible Materials"[tiab] OR "Alloplastic"[tiab] OR "Biomaterials"[tiab] OR "Biomimetic Materials"[Mesh] OR "Biomimetic Materials"[tiab])).
Outcome	(("toxicity"[Subheading] OR "toxicity"[tiab] OR "neurotoxic"[tiab] OR neurotoxic*[tiab] OR "Neurotoxicity"[tiab] OR "Neurotoxicity Syndromes"[Mesh] OR neuropath*[tiab] OR "Hypersensitivity"[Mesh] OR "Hypersensitivity"[tiab] OR "Meningitis"[Mesh] OR "Meningitis"[tiab] OR "Foreign–Body Reaction"[Mesh] OR "Foreign–Body Reaction"[tiab] OR "Foreign body "[tiab] OR "Allergy and Immunology"[Mesh] OR "Allergy" [tiab] OR inflamm*[tiab] OR "Inflammation"[Mesh] OR "Neurogenic Inflammation"[Mesh] OR "Arachnoiditis"[Mesh] OR "Arachnoiditis"[tiab] OR "Nervous System Diseases"[Mesh] OR "Nervous System Diseases"[tiab] OR "Central Nervous System Diseases"[Mesh] OR "Central Nervous System Diseases"[tiab] OR "Graft Rejection"[Mesh] OR "Graft Rejection"[tiab] OR "Encephalitis"[Mesh] OR "Encephalitis"[tiab] OR "Granuloma"[Mesh] OR "Granuloma, Foreign–Body"[Mesh] OR "Gliosis"[Mesh] OR "Granuloma"[tiab] OR "Granuloma, Foreign–Body"[tiab] OR "Gliosis"[tiab]))

Table 3
Inclusion and exclusion criteria.

Inclusion criteria:	Exclusion criteria:
1. Aseptic (chronic) inflammation	1. Type of literature: - Summary articles - Technical notes - Letter to editors - Opinions or commentaries without original data. - Book chapter
2. Implant exposure without pathogen contamination.	2. Complications specific to the operation
3. Allergic/hypersensitivity reaction	3. Stated or identified infection or septic inflammation
4. Toxicity	4. Cases involving autologous bone
5. Identified diagnostic method for points 2, 3, and 4 of the inclusion criteria	5. Inflammation diagnosed through imagery
6. Cranioplasty involving any part of the calvaria	6. In vitro studies
7. Implants and onlay cranioplasty	7. Animal studies
	8. Articles studying osseointegration only

2015; Moser et al., 2017; Al-Afif et al., 2018; Hirohi et al., 2018), a total of 18 patients endured cranioplasty material-based toxicity. These comprized six males, seven females and five of unknown sex aged 16–68 years (age unknown in three studies) (Table 4a). The PMMA cranioplasty fabrication technique was unspecified in six studies, while in three studies the indirect molding technique was performed (Tysvaer and Hovind, 1977; Wurm et al., 2004; Brett-Major et al., 2008; Moser et al., 2017; Hirohi et al., 2018). The direct application of PMMA for restoring a cranial defect was performed in one study (Pikis et al., 2015). The prime indication for craniectomy was meningioma (five cases, 28%), followed by trauma (two cases, 11%). One study mentioned the use of a PMMA onlay implant for aesthetic indication (Hirohi et al., 2018). The time between craniectomy and cranioplasty was reported in four studies and varied between immediate implant application and 13 months. Toxic events occurred intraoperatively until 29 months after cranioplasty (Table 4b).

Various types of toxic reaction were observed for PMMA cranioplasties. Hypersensitivity and allergic reactions occurred in four patients (22%). Meel (2004) reported a fatal type III allergic/hypersensitivity reaction 29 months after a frontal bone PMMA cranioplasty (brand not mentioned). This allergic reaction reached the subdural and subarachnoid area, the brain, the lower limbs, pericardium, and pleura. Two studies (Brett-Major et al.,

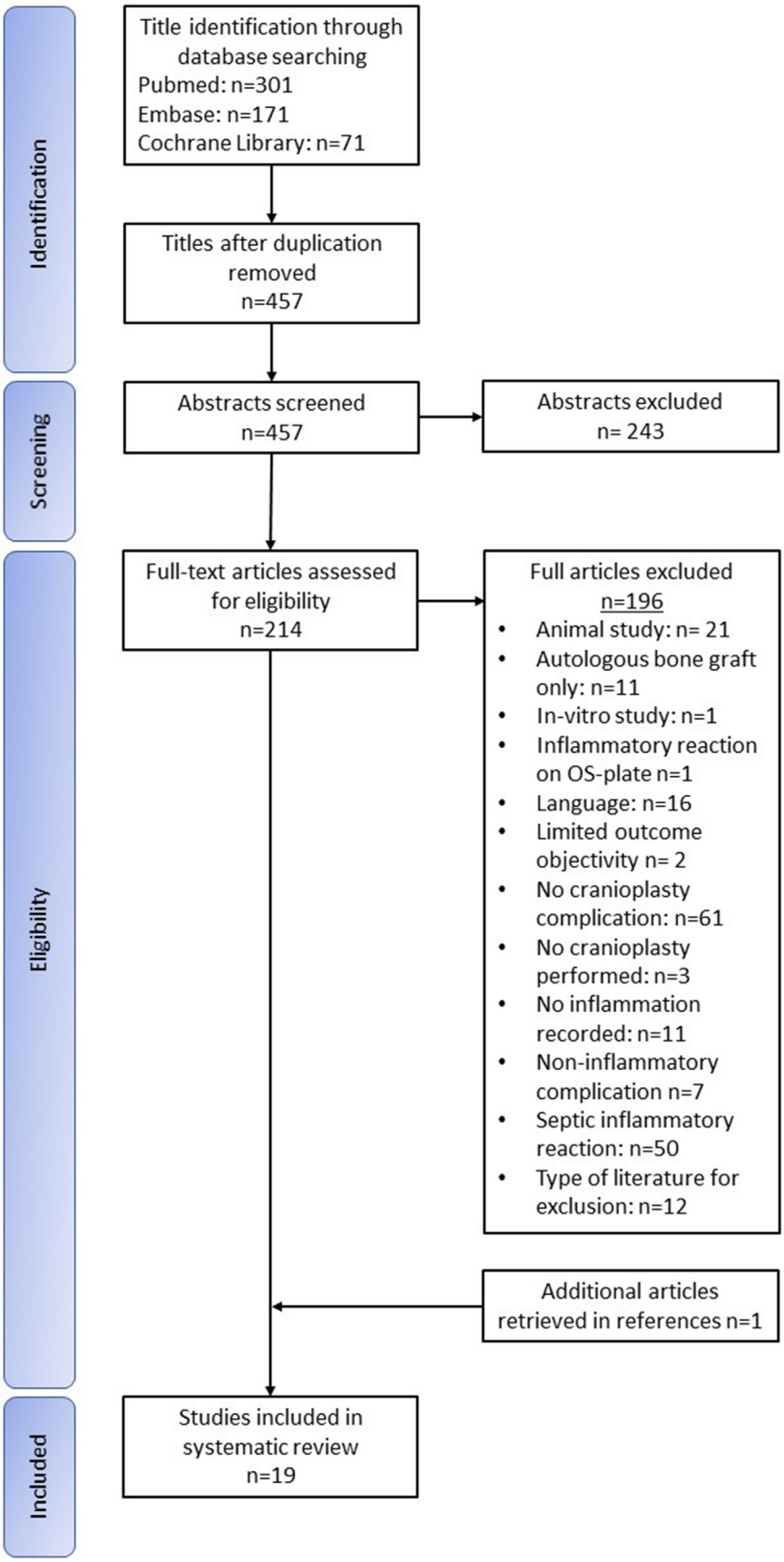

Fig. 1. PRISMA-P-based flow chart for the systematic literature search. OS = osteosynthesis.

Table 4a
Extracted data.

Author, Year	Study type	Materials used + fabrication technique	Subjects/CP	Subjects/CP with toxicity	Sex	Age (years)	Implant /onlay	CT indication	Operation before CT	Location of CP
Acylic/polymer/PMMA (9)										
Tysvaer and Hovind (1977)	Retrospective	Stainless steel combined acrylic Indirect technique	24	1	NM	NM	Implant	NM	NM	NM
Yoshii et al. (2001)	Case report[a]	PMMA Technique NS	1/2	1/2	M	39	Implant	Intracerebral hemorrhage	–	Temporal
Meel (2004)	Post-mortem case report	PMMA Technique NS	1	1	M	NM	Implant	Trauma	–	Frontal
Wurm et al. (2004)	Retrospective	Carbon fiber reinforced polymer (epoxy resin matric) Indirect technique	37/41	1	M	25	Implant	Aneurysm	–	NM
Brett-Major et al. (2008)	Case report	PMMA Indirect technique	1	1	F	57	Implant	Traumatic subdural hematoma	Autologous bone graft	Fronto-temporal
Gautschi et al. (2010)	Case report	PMMA Technique NS	1	1	F	39	Implant	NM	NM	Parieto-occipital
Pikis et al. (2015)	Retrospective	PMMA (Gelfoam on dura) Direct technique	6	6	3 × F 3 × M	16–66	Implant	2 × CPA meningioma 2 × CPA epidemoid 1 × AN 1 × occipital LCH 1 × meningioma	–	4 × RS 1 × occipital 1 × parietal
Moser et al. (2017)	Retrospective	PMMA Indirect technique (PALACOS R)	17	1	F	49	Implant	NM	NM	NM
Al-Afif et al. (2018)	Retrospective	PMMA Technique NS	1	1	F	68	Implant	Meningioma	NM	Frontal
Hirohi et al. (2018)	Retrospective	PMMA Indirect technique	75	4	NM	NM	Onlay	–	–	Frontal ± temporal
		Total	**164/169**	**18 (11.0%)/19 (11.2%)**						
Titanium (3)										
Hettige and Norris (2012)	Post-mortem case report	Titanium NS	1	1	F	64	Implant	Olfactory groove meningioma	–	Bifrontal
Sinkin et al. (2015)	Case report	Titanium (mesh)	1	1	F	65	Implant	AN	–	RS
Sun et al. (2018)	Prospective study	Titanium alloy	207	4	NM	NM	Implant	NM	–	NM
		Total	**209**	**6 (2.9%)**						
Calcium Phosphate (3)										
Foster et al. (2016)	Retrospective	CaP (CRANIOS REINFORCED or HYDROSET)	336	1	NM	NM	Implant	Tumor or cranial nerve neuralgia	–	RS
Pourdanesh et al. (2018)	Case report	CaP (JECTOS)	1	1	F	28	Implant	Trauma	–	Anterior frontal sinus wall
Chen et al. (2018)	Retrospective	CaP HA ceramic	57	1	NM	NM	Implant	NM	NM	NM
		Total	**394**	**3 (0.8%)**						
PEEK (1)										
Kearney et al. (2018)	Retrospective	PEEK	1	1	M	40	Implant	Oligodendroglioma	–	Frontal
		Total	**1**	**1**						
Others (2)										
Andrzejak et al. (2005)	Retrospective	Polypropylene-polyester knit (CODUBIX)	275	7	NM	NM	Implant	NM	No	NM
Choudhry et al. (2013)	Retrospective	Two thin polyethylene layers enveloping a titanium mesh (MEDPOR TITAN)	98	1	NM	NM	Implant	NM	–	Frontotempo-ral and orbitozygom-atic
		Total	**373**	**8 (2.1%)**						

Abbreviation: AN = acoustic neuroma, CaP = calcium phosphate, CPA = cerebellopontine angle, CT = traniectomy, CP = pranioplasty, F = female, HA = hydoxyapatite, LCH = Langerhans cell histiocytosis, M = male, Me = mentioned, NM = not mentioned, NS = not specified, PEEK = polyether ether ketone, PMMA = polymethylmethacrylate, RS = retrosigmoid.

[a] In this particular study two consecutive PMMA cranioplasty implants were performed in one patient. Both failed due to toxicity.

Table 4b
Extracted data.

Author, Year	Time lapse between CT and CP	Time lapse between CP and toxicity	Sinus involvement	RT	Type of toxicity	Examination of toxicity	Treatment
Acylic/polymer/PMMA (9)							
Tysvaer and Hovind (1977)	NM	NM	NM	NM	Aseptic inflammatory reaction	Aseptic exudate production	Ablation of the implant
Yoshii et al. (2001) [a]	1. 4 months 2. 13 months	1.6 weeks 2.3 months	No	No	1. Chronic aseptic inflammation 2. Chronic aseptic inflammation	1. Swelling and aseptic aspiration 2. Swelling + trismus; PE of the cicatrix around the coronoid process; infiltration of eosinophils in fibrotic tissue; slightly elevated CRP (43 mg/L); negative MM patch test.	1. Implant ablation and reconstruction with PMMA implant 2. Implant and coronoid process ablation (to increase mouth opening)
Meel (2004)	During the craniectomy	29 months	NM	No	Fatal type III hypersensitivity reaction	Postmortem PE of multiple organs; systemic deposition of antigen–antibody complexes	–
Wurm et al. (2004)	9 months	NM	Yes	No	Allergic reaction	PE: allergic granulomatous tissue with histiocytes and carbon particles	Ablation of the implant and restoration with same implant
Brett-Major et al. (2008)	NM	2 weeks	NM	No	Intracranial foreign body	PE: eosinophilic and granulomatous inflammation of the dura Mild absolute eosinophilia (900 cells per mm^3) No infection was objectified	Debridement of the implant
Gautschi et al. (2010)	NM	42 days	No	No	Allergic reaction	Elevated eosinophils (12.3%), aseptic wound, and positive MM skin patch test	Implant ablation and replacement with ceramic CaP CP
Pikis et al. (2015)	NM	Intraoperatively	NM	No	Nerve palsies Awakening problems Partially recovered nerve damage	Intraoperative neurological monitoring: disappearance of BAER wave × 1, cranial nerve palsy × 1 Confusion, delayed awakening, and restlessness × 3 Partially recovered hemianopia × 1 and left foot numbness × 1	–
Moser et al. (2017)	NM	53 days	NM	No	Chronic wound healing	No infection identified	Debridement and split skin graft
Al-Afif et al. (2018)	NM	45 years	NM	No	Intracranial FBR	Neuro-PE: foreign body granuloma	NM
Hirohi et al. (2018)	–	NM	No	No	Acne-like rash, which subsided after 6 months	No infection mentioned	–
Titanium (3)							
Hettige and Norris (2012)	NM	Intraoperatively	Yes	No	Fatal allergic reaction	Post-mortem PE: brain swelling, diffuse brain necrosis, and elevated mast cell tryptase	–
Sinkin et al. (2015)	NM	NM (years prior)	No	NM	Allergic reaction	Headaches, scalp swelling and rash Positive patch test for titanium	Implant ablation and replacement with PMMA CP implant
Sun et al. (2018)	NM	NM	NM	NM	Implant exposure	Aseptic wound culture	Implant ablation and tissue debridement
Calcium phosphate (3)							
Foster et al. (2016)	NM	1 month	No	NM	Edematous, swollen wound	Surgical wound exploration and aseptic wound culture	NM
Pourdanesh et al. (2018)	During craniectomy	4 months	Yes	No	Aseptic fistula originating from a FBR	PE of fistulectomy: granulation tissue and giant cells	Implant ablation and resonation with calvarial autograft
Chen et al. (2018)	NM	NM	NM	NM	Epifolliculitis leading to skin necrosis and implant exposure	No infection mentioned	Debridement of implant and overlaying soft tissue

Table 4b (*continued*)

Author, Year	Time lapse between CT and CP	Time lapse between CP and toxicity	Sinus involvement	RT	Type of toxicity	Examination of toxicity	Treatment
PEEK (1)							
Kearney et al. (2018)	NM	23 months[b]	No	No	Intracranial FBR	PE: histology and immunohistochemistry showed astrocytic gliosis and lymphocyte and macrophage infiltration	NM
Others (2)							
Andrzejak et al. (2005)	NM	NM	NM	No	Aseptic inflammation	No infection identified	NM
Choudhry et al. (2013)	NM	NM	No	NM	Idiopathic inflammatory response	No infection was identified	Implant ablation

Abbreviations: BAER = brainstem auditory evoked response, CT = craniectomy, CP = cranioplasty, CRP = C-reactive protein, FBR = foreign-body reaction, MM = methylmethacrylate, NM = Not mentioned, NS = not specified, PE = pathological examination, PEEK = polyether ether ketone, PMMA = polymethylmethacrylate, RT = radiotherapy (pre- or postoperative).

[a] In this particular study two consecutive PMMA cranioplasty implants were performed in one patient. Both failed due to toxicity.

[b] Control MRI scan demonstrating radiological suspicion of tumor recurrence. The patient was asymptomatic.

2008; Gautschi et al., 2010) each presented a case with elevated eosinophil blood count a few weeks after the insertion of a PMMA cranioplasty (brand not mentioned). Both cases presented an aseptic inflammatory fluid collection near the implant, but only one presented a postoperative positive skin-patch test (Gautschi et al., 2010). Wurm et al. (2004) combined carbon fiber with epoxy resin manufactured using a mold (brand not mentioned). Due to slight perioperative trimming of the cranioplasty, one patient endured an allergic reaction to the carbon particles (non-specified granuloma with incorporation of histiocytic cells with the carbon particles).

Chronic aseptic inflammation occurred in eight other patients. One retrospective case series (Tysvaer and Hovind, 1977) assumed that the accumulated subdermal aseptic exudate above a combined acrylic/titanium mesh plate cranioplasty (brand not mentioned) resulted from a reaction to acrylic. Yoshii et al. (2001) presented a patient who endured chronic aseptic muscle tissue scarring, characterized twice after two consecutive PMMA cranioplasties (brand not mentioned) to reconstruct a temporal defect. Interestingly, the skin-patch test was negative for this patient. After intraoperative reshaping of a PMMA cranioplasty (PALACOS R, Heraeus Medical GmbH, Wehrheim, Germany), one case presented with aseptic chronic wound healing (Moser et al., 2017). Intracranial FBR occurred 45 years after PMMA cranioplasty (brand not mentioned) indicated after a meningioma resection (Al-Afif et al., 2018). Spontaneous acne-like rashes developed on the foreheads of four patients who requested aesthetic forehead contouring with a PMMA onlay cranioplasty (brand not mentioned) (Hirohi et al., 2018). The onlay implants were sculpted preoperatively to prevent intraoperative contouring.

Lastly, Pikis et al. (2015) convincingly argued for PMMA as the cause of observed neurotoxicity associated with cranioplasty implants (brand not mentioned) in a retrospective case series of six cases. In four cases where a PMMA cranioplasty was performed after a retrosigmoid approach, delayed awakening and restlessness occurred. In one of these four cases, the brainstem auditory evoked response disappeared, while another patient endured a transient (contralateral to the operative site) cranial nerve III and IV palsy. The fifth PMMA cranioplasty patient developed partial hemianopsia after extirpation of an occipital bone Langerhans cell histiocytosis (without manipulation of the cerebral cortex). The last patient retained a partially recovered left dorsal foot numbness after cranioplasty for a right-sided intra-osseous meningioma without dural opening.

3.3.2. Titanium (commercially pure or alloy)

Chronic inflammation or allergic reaction due to titanium cranioplasty toxicity appeared in five patients within two case reports (Hettige and Norris, 2012; Sinkin et al., 2015) and one retrospective series (Sun et al., 2018). The two case reports mentioned sex (both female), age (64 and 65 years), indication for craniectomy (meningioma and acoustic neuroma), and location of cranioplasty (bifrontal and retrosigmoid) (Table 4a).

Hettige and Norris (2012) reported an intraoperative fatal type I allergic reaction to titanium (brand and grade not mentioned). The 64-year-old female died immediately after awakening from anesthesia. Postmortem examination determined diffuse brain swelling as the cause of death. Early signs of necrosis were seen in the midbrain and basal ganglia. Elevated mast cell tryptase was found by blood analysis. Sinkin et al. (2015) present a case of scalp rash with concurrent soft tissue swelling several years after a titanium mesh implant (brand and grade not mentioned). The skin-patch test was positive for a titanium (grade not mentioned) type IV allergy.

The use of skin-patch tests to identify allergies to titanium used for cranioplasty was studied by Sun et al. (2018). This included 207 patients undergoing full-thickness titanium alloy implants (brand not mentioned). Pre- and postoperative skin-patch testing for multiple metals was carried out. Eleven patients experienced implant exposure. In four cases, infection was not identified. None of the 11 patients showed hypersensitivity to titanium, and negative results to all tested metals suggested a lower risk of titanium implant failure ($p < 0.001$). Hypersensitivity to several types of metal – four or five in particular – resulted in a statistically significant higher risk of developing implant failure. Cobalt was the only metal with a significantly positive relationship with implant failure (Sun et al., 2018).

3.3.3. Calcium phosphate

A total of three cases, appearing in two retrospective studies (Foster et al., 2016; Chen et al., 2018) and one case report (Pourdanesh et al., 2018), presented with toxic reactions to a derivative of CaP. Patient and operation characteristics were described in the case report by Pourdanesh et al. (2018) (Table 4a).

In one patient, Foster et al. (2016) surgically explored an edematous, swollen aseptic wound 1 month after CaP cement cranioplasty (brand not specified; two types of CaP were used – CRANIOS REINFORCED, Synthes, Inc., West Chester, Pennsylvania, USA and HYDROSET, Stryker, Kalamazoo, Michigan, USA) to close a

retromastoid defect. Pourdanesh et al. (2018) reported a patient with midfrontal fistula without bacterial growth, but with aseptic effusion 4 months after receiving a titanium mesh (grade not mentioned) enveloped with a CaP cement derivative (JECTOS; dehydrated dicalcium phosphate; Kasios, Launaguet, France) for the reconstruction of the anterior table of the frontal sinus. One patient suffered from repeated epifolliculitis adjacent to the ceramic hydroxyapatite (a type of CaP) cranioplasty (brand not mentioned), which eventually led to skin necrosis (Chen et al., 2018).

3.3.4. PEEK

In a retrospective study, Kearney et al. (2018) described one case of a PEEK cranioplasty (brand not mentioned) who endured an intracerebral FBR characterized by oligodendrocyte hyperplasia, reactive astrocytic gliosis, and macrophage infiltration.

3.3.5. Other materials

Two studies presented material-based toxicity from alternatives to the abovementioned and less popular materials. Andrzejak et al. (2005) presented the clinical outcomes of 275 patients receiving polypropylene-polyester plates (CODUBIX, Tricomed, Łódź, Poland) to reconstruct calvarial defects, with 22 patients suffering from inflammation at the implantation site. In seven patients, the cause of inflammation was not found, rendering it to be an aseptic reaction and not an infection. Choudhry et al. (2013) presented the results for 98 patients receiving titanium mesh implants enveloped with a polyethylene sheet (MEDPOR TITAN, Stryker, Kalamazoo, Michigan, USA) to reconstruct a frontotemporal defect. One patient developed an idiopathic and very probable aseptic inflammatory response, which required removal of the implant.

3.4. Risk of bias

A total of 11 studies (57.9%) showed a high risk of bias. Seven had a moderate risk (36.8%), and only one a low risk of bias (5.3%). The average score was 7.4, which represents a high risk of bias.

4. Discussion

Toxic reaction to an implant may lead to explantation and make treatment more problematic. Therefore, we have tried to illuminate material-based (aseptic) toxicity by comparing materials used for cranioplasties.

Publications on PMMA, CaP, PEEK, and titanium implants causing material-based toxicity were identified for this review. Aside from these materials, polyethylene alone and alumina (aluminum oxide) have also been described for cranioplasty. Porous polyethylene shows good ingrowth of bone and neovascularization (Khader and Towler 2016; Piazza and Grady, 2017), while aluminum oxide (a type of ceramic) is used for its strength and good aesthetic results (Shah et al., 2014; Khader and Towler, 2016; Alkhaibary et al., 2020). Although the latter two materials are frequently used, our review did not allow identification of reports on their ability to induce an aseptic toxic reaction. However, this does not imply that they are safer compared with the materials included in this systematic review.

Material toxicity occurs in a variety of forms, including allergic reaction, CIR, FBR, and neurotoxicity. In five studies (Moser et al., 2017; Sun et al., 2018; Foster et al., 2016; Andrzejak et al., 2005; Choudhry et al., 2013), chronic wounds leading to cranioplasty exposure were assessed for infection, which could not be identified. Consequently, we classified these results as chronic aseptic inflammation. A total of 50 articles were excluded because septic inflammatory reaction was mentioned (Fig. 1). Often, implant exposure was scored as 'infection' due to bacterial contamination based on positive swab collections from the exposed implant. As stressed by Sun et al. (2018), this practice is questionable. Contamination of the implant may very well be secondary to implant exposure that has been caused by toxicity to, and breakdown of, adjacent soft tissues (Sun et al., 2018). In their study, implant failure occurred between 13 weeks and 11 months after cranioplasty, which according to the authors exceeded the time for an infection. In a systematic review conducted by Van de Vijfeijken et al. (2018), PMMA had the highest rates of infection (7.8%), with implant failure occurring in 7.9%. However, the method of identifying infection was not mentioned. It is paramount to make a distinction between infection and aseptic inflammation, although these are difficult to distinguish. Therefore, comparative animal studies are needed to identify soft- and hard−tissue reactions to specific materials. Furthermore, the difficulty in making this distinction may have caused an underestimation of the material toxicity experienced during cranioplasties because some were misreported as infections.

A T-cell mediated type IV allergic/hypersensitivity reaction is the most commonly reported reaction among titanium (alloy) and acrylic derivative implants. This was shown to lead to explantation in four studies (Wurm et al., 2004; Brett-Major et al., 2008; Gautschi et al., 2010; Sinkin et al., 2015). Therefore, prevention is of utmost importance. Screening for type IV allergies to titanium (alloy) or acrylic is performed by gathering medical history (prior sensitization) and skin-patch testing (Spencer et al., 2016; Goutam et al., 2014). In orthopedic surgery, prior sensitization to the abovementioned materials (used in dental fillers, dental implants, cosmetic products, etc.) should be considered when choosing a material (Goutam et al., 2014; Gamez, 2015; Thomas and Summer, 2017). However, even with a negative medical history, cranioplasty materials themselves can still be the source of sensitization, as established by Sun et al. (2018), possibly leading to implant failure. Currently, there is a lack of substantial evidence for a positive relationship between medical history and implant failure, and it therefore remains doubtful. A material should not be used in cases of prior allergic reaction.

The importance of skin-patch test results also remains questionable. In our review, true positives were assessed for acrylic (Gautschi et al., 2010) and titanium (grade not mentioned) (Sinkin et al., 2015). In contrast, Yoshii et al. (2001) presented a false negative skin-patch test case. In the literature, skin-patch testing has produced controversial results because patients with positive skin-patch tests often tolerate their titanium implants (Thomas, 2014; Thomas and Summer, 2017). An explanation for this is the difference in immunological behavior between skin and bone (Goutam et al., 2014). The range of metals used in titanium alloys makes skin-patch testing difficult to interpret (Sun et al., 2018).

In view of the above, multicentric high-volume studies are needed to find the correct screening techniques to prevent material-based allergic reactions in cranioplasty surgery.

In addition to the aforementioned problems associated with screening, titanium allergies show low prevalence (Goutam et al., 2014). Moreover, PMMA type IV allergy incidence has not been well reported in the literature and may therefore be underdiagnosed in cranioplasty surgery. Meel (2004) presented a fatal case of type III allergic reaction to a PMMA cranioplasty, whereas in the case reported by Hettige and Norris (2012), the patient died of a very probable type I allergic reaction to a titanium implant (grade not mentioned). A literature search did not identify tools for screening for these types of allergic reaction, but fortunately they seem to be quite rare.

CaP derivatives are among the main components of human bone, and therefore allergic reactions are not possible. This is not the case for PEEK. Two studies presented delayed type IV allergic

reactions to PEEK implants (intervertebral cage implant and self-anchoring device used to reattach a rotator cuff) (Maldonado-Naranjo et al., 2015; Kofler et al., 2017). In each case this was due to a cross-reaction to bisphenol, which is also found in the resin, to which the patient was known to be allergic. Further studies should evaluate the risk of PEEK allergies in cases of prior resin sensitization.

The implantation of biomaterials spontaneously initiates an acute inflammatory reaction, which leads to a CIR. If the CIR does not attenuate after 2 weeks, it becomes pathological, and inflammation is transferred to adjacent tissues (Anderson et al., 2008; Sheikh et al., 2015). This timeframe was respected in the eight studies we included in our systematic review, in which CIR occurred 30–53 days after implantation (Tysvaer and Hovind, 1977; Yoshii et al., 2001; Andrzejak et al., 2005; Choudhry et al., 2013; Foster et al., 2016; Moser et al., 2017; Chen et al., 2018; Hirohi et al., 2018). As presented in Table 4b, there were different clinical manifestations of CIR. In addition to sterile implant exposure (Andrzejak et al., 2005; Choudhry et al., 2013; Foster et al., 2016; Moser et al., 2017), CIR manifested as aseptic exudate (Tysvaer and Hovind, 1977), an acne-like reaction (Hirohi et al., 2018), muscle scarring (Yoshii et al., 2001), and epifolliculitis (Chen et al., 2018).

Following an unresolved CIR, a FBR occurs, which is characterized by monocytes, macrophages, and foreign-body giant cells at the biomaterial interface. Eventually, the granulation of tissue forms a fibrous capsule around the biomaterial, separating it from the body (Anderson et al., 2008; Sheikh et al., 2015). Our review included three studies that identified both extra- and intracranial FBRs to implant cranioplasty (Pourdanesh et al., 2018; Al-Afif et al., 2018; Kearney et al., 2018). Besides displaying neurotoxicity (Kearney et al., 2018), intracerebral FBR can be misdiagnosed by MRI as recurrent brain neoplasia, leading to unnecessary chemo- or radiotherapy.

The causes of toxicity leading to CIR and FBR differ between materials. For acrylic-based materials (polymer or PMMA), residual monomer generates toxicity. In vitro studies have demonstrated the cytotoxic effects of the PMMA monomer (Jorge et al., 2003; Goiato et al., 2015). The number of residual monomers formed, and the subsequent level of cytotoxicity (Goiato et al., 2015), relate to the method of polymerization. For instance, autopolymerization releases more monomers when compared with other types of polymerization (heat, microwave, or light) (Ata and Yavuzyilmaz, 2009; Ebrahimi Saravi et al., 2012). Due to its malleability, the direct application of PMMA onto the defect is an old technique that is still performed today (Kwarcinski et al., 2017). PMMA in direct contact with the dura can lead to an inherent issue with tissue acceptability. For instance, to cool the exothermic polymerization reaction, cold saline is constantly irrigated onto the cranioplasty (Marchac and Greensmith, 2008; Lee et al., 2009). However, the irrigation may disperse residual monomers into the brain, risking neurotoxicity. According to Pikis et al. (2015), this is a likely cause of nerve damage on the contralateral side of the operating field and neurosymptomatic awakening. This is the first study to raise awareness of possible neurotoxicity or neuro-irritability resulting from residual monomers. The majority of studies using PMMA do not mention these types of 'minor' intraoperative neurological reaction. We can therefore assume this complication to be underestimated in the literature. In many cases where craniectomy is required for decompression of intracranial bleeding, a malignant tumor, or trauma, patients are often left with neurological deficits that are related to the primary disease or issue. As such, pre-existing neurological impairment may mask the true neurotoxic effects of the biomaterial used.

As a result of extensive exothermic reaction damage (Golz et al., 2010) and residual monomer irrigation, direct molding has been replaced by an indirect approach (Cheng and Wee, 1999), whereby a mold representing the shape of the defect (or resected bone) is filled with PMMA (Origitano et al., 1995; Caro-Osorio et al., 2013; Abdel Hay et al., 2017; Cheng et al., 2018). However, as explained by Moser et al. (2017), PMMA cranioplasties fabricated with the indirect technique may still need fine shaping when the implant does not fit, and holes are drilled for screw fixation. These adjustments to the molded PMMA implant may release residual monomers and cause CIR, as presented by Moser et al. (2017). Moreover, during intraoperative production of PMMA, inaccurate mixture concentrations of liquid and monomer can lead to a greater amount of residual monomer (Jorge et al., 2003). Interestingly, Hirohi et al. (2018) reported four patients who suffered a late acne-like rash after prefabricated onlay PMMA cranioplasty. Intraoperative reshaping did not occur, providing evidence that an immaculate PMMA cranioplasty can induce an inflammatory reaction.

Alternatives to PMMA have also been shown to induce certain local or systemic reactions. CaP is useful because it promotes osseointegration into the surrounding cranium (Eliaz and Metoki, 2017; Ono et al., 2017). CaP derivatives are minerals that make up the human bone and should therefore be biocompatible (Jeong et al., 2019). However, in two studies, a CaP cement derivative caused CIR and FBR (Foster et al., 2016; Pourdanesh et al., 2018). In one rabbit study, 45S5 BIOGLASS (Novabone-C/M, Porex Surgical, Newnan, Georgia, USA) – a CaP cement derivative – was implanted in a calvarial defect. Small particles migrated into the dura, generating local inflammatory reactions followed by an FBR (Moreira-Gonzalez et al., 2005). Chen et al. (2018) reported the case of a ceramic hydroxyapatite implant that led to CIR (epifolliculitis and skin necrosis). Osseointegration of ceramic implants is time consuming and often incomplete, which creates susceptibility to microfractures (Spennato et al., 2020). As mentioned above, the migration of these particles can lead to CIR in the adjacent tissues. When ceramic CaP cement is used to restore a cranial defect, calvarial protection needs to be implemented.

One study demonstrated intracerebral FBR to PEEK (Kearney et al., 2018). PEEK is supposed to be bioinert and therefore safe for cranioplasty surgery (Zanotti et al., 2016). However, PEEK implants inserted into the tibiae of mature New Zealand white rabbits elicited proinflammatory M1 macrophage immune responses in surrounding bone 10 and 28 days after the procedure (Trindade et al., 2018, 2019). However, no study has shown long-term immune responses to PEEK, which makes this material safe for cranioplasty implants.

Of the lesser known materials, polyethylene and polypropylene-polyester have been shown to induce CIR when used as cranioplasty implants (Andrzejak et al., 2005; Choudhry et al., 2013). Polypropylene meshes induced local CIR and FBR when used for transvaginal and inguinal hernial repair (Thomas et al., 2018; Heymann et al., 2019). Recently, a study in mice demonstrated an intense foreign-body giant cell reaction 6 months after subcutaneously implanting porous polyethylene (Vollkommer et al., 2019). Histological findings for 10 facial polyethylene explants showed chronic inflammation and foreign-body giant cells in almost all cases (Gosau et al., 2008). The rare use of polypropylene-polyester and polyethylene for cranioplasty implants makes it difficult to assess their safety.

4.1. Appraisal of this systematic review

Based on this systematic review, classification of materials as toxic in cranioplasty surgery must be done with care, as only one of the 19 included studies had a low risk of bias (Table 5a–b). The high

Table 5a
Quality assessment.

Author, year	*Hypothesis explained*	*Participant characteristics*	*Multic entric*	*Eligibility criteria*	*Consecutive patients recruited*	*Similar location of disease*	*Prospective study*	*Intervention explained*	*Additional interventions explained*	*Outcome measures established a priori*
Acylic/polymer/PMMA										
Tysvaer, 1977	Yes	Yes	No	Unclear	Unclear	Unclear	No	Unclear	No	No
Yoshii, 2001	No	Yes	No	No	No	No	No	Yes	No	No
Meel, 2004	Yes	Unclear	No	No	Unclear	No	No	Unclear	No	No
Wurm, 2004	Yes	Yes	No	Yes	Unclear	No	Yes	Yes	No	No
Brett-Major, 2008	No	Unclear	No	No	No	No	No	Yes	Yes	No
Gautschi, 2010	No	Unclear	No	No	No	No	No	Unclear	No	No
Pikis, 2015	Yes	Yes	No	No	No	No	No	Yes	No	No
Moser, 2017	Yes	Yes	No	Yes	No	Unclear	No	Unclear	No	No
Al-Afif, 2018	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes
Hirohi, 2018	Yes	Unclear	No	Unclear	Unclear	Yes	No	Yes	Yes	No
Titanium										
Hettige, 2012	No	Unclear	No	No	No	No	No	Unclear	No	No
Sinkin, 2015	No	Unclear	No	No	No	No	No	Unclear	No	No
Sun, 2018	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes
Calcium phosphate										
Foster, 2016	Yes	Unclear	No	Yes	Unclear	Unclear	No	Yes	No	Yes
Pourdanesh, 2018	No	Yes	No	No	Unclear	No	No	Yes	No	No
Chen, 2018	Yes	Unclear	No	No	No	No	No	Unclear	No	No
PEEK										
Kearney, 2018	Yes	Unclear	No	Yes	No	No	No	Yes	No	Yes
Other										
Andrzejak, 2005	No	Unclear	No	Yes	Unclear	No	No	Yes	No	No
Choudhry, 2013	Yes	Unclear	No	Yes	Yes	No	No	Yes	No	No

Abbreviations: PEEK = polyether ether ketone, PMMA = polymethylmethacrylate

and moderate risks of bias were due to the retrospective nature of the case series. Patients were not recruited consecutively or included at a similar stage of their disease. All studies were monocentric. Outcome measures were seldomly established a priori, measured before and after the operation, assessed blindly, or interpreted statistically. Random variability was not assessed. In addition, more than half of the studies were case reports, reflecting a high risk of bias.

An explanation for the high incidence of toxic morbidities for PMMA may lie in the fact that this material is the one most often used in cranioplastic surgery. This may also explain the diversified toxicity to PMMA (allergic reactions, CIR, FBR, and neurotoxicity).

The location of the defect may have an influence on the severity of a CIR. Six of the 18 studies presented a frontal bone defect (Table 4a). The thinner soft tissue covering the frontal bone may be a risk factor for implant exposure when toxic materials are used. Animal studies should give a clearer view on the effect of material toxicity with regard to the thickness and the type of soft tissues covering the cranial vault. In the literature, cranioplasty implants that involved the frontal sinus were contra-indicated due to bacterial contamination (Verret et al., 2005). Frontal sinus involvement was cited in three articles (Table 5a, b). Two presented an allergic reaction to the implant, and the third presented an aseptic fistula originating from an FBR. This implies material-based toxicity rather than septic contamination by sinus flora microorganisms.

Table 5b
Quality assessment.

Author, Year	*Objective outcome measure*	*Outcome measured before and after intervention*	*Blind outcome assessment*	*Statistical test on outcome*	*Follow-up length reported*	*Loss in follow-up reported*	*Random variability estimated*	*Adverse events reported*	*Result-supported conclusions*	*Competing interests stated*	*Score – ROB*
Acylic/polymer/PMMA											
Tysvaer, 1977	Yes	No	No	No	No	No	No	Yes	No	No	4 – high
Yoshii, 2001	Yes	No	No	No	Yes	No	No	Yes	Yes	No	7 – high
Meel, 2004	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	6 – high
Wurm, 2004	Yes	No	No	No	Yes	No	No	Yes	Yes	No	9 – moderate
Brett-Major, 2008	Yes	No	No	No	Yes	No	No	Yes	Yes	No	6 – high
Gautschi, 2010	Yes	No	No	No	No	No	No	Yes	Yes	No	3 – high
Pikis, 2015	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	9 – moderate
Moser, 2017	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	9 – moderate
Al-Afif, 2018	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	10 – moderate
Hirohi, 2018	No	No	No	No	Yes	Yes	No	Yes	No	Yes	8 – high
Titanium											
Hettige, 2012	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	5 – high
Sinkin, 2015	Yes	No	No	No	Yes	No	No	Yes	Yes	No	4 – high
Sun, 2018	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	16 – low
Calcium phosphate											
Foster, 2016	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	10 – moderate
Pourdanesh, 2018	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	7 – high
Chen, 2018	No	No	No	No	Yes	Unclear	No	Yes	Yes	No	4 – high
PEEK											
Kearney, 2018	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes	10 – moderate
Others											
Andrzejak, 2005	Yes	No	No	No	Yes	No	No	Yes	Yes	No	6 – high
Choudry, 2013	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	9 – moderate

Abbreviations: ROB = risk of bias, PEEK = polyether ether ketone, PMMA = polymethylmethacrylate

The time between craniectomy and cranioplasty may influence the type of inflammation. A short duration between the two procedures may lead to infection (Cho and Kang, 2017). Cranioplasties were performed from the time of the initial craniectomy up to 9 months later. According to recent literature, the incidence of postoperative infection does not differ between early (<90 days) or late (>90 days) cranioplasty (Bjornson et al., 2019; Malcolm et al., 2016). Inflammation of early cranioplasty therefore may also be attributed to aseptic inflammation.

Although it was not mentioned in any of the included articles, preoperative radiotherapy has been reported to carry an almost seven-fold increased risk for postoperative complications (Reddy et al., 2014). Preoperative radiotherapy may be a confounding factor in aseptic inflammatory reaction statistics.

5. Conclusion

We have presented objective evidence that material-based toxicity is a real threat in cranioplasty surgery. According to our systematic review, adjacent and distant tissues to PMMA cranioplasty may be more at risk of suffering material-based toxicity. Residual monomers, which originate from directly and indirectly fabricated PMMA cranioplasty, may induce distant toxic reactions that can lead to neurotoxicity. PMMA may also induce hypersensitivity reactions, but this is difficult to screen. Therefore, we advise surgeons to remain cautious when using this material. CaP is known to be a safe material when correctly manipulated during the operation. Although rare, allergic reactions to titanium (with only one article mentioning titanium alloy) have been described, and preoperative screening should be performed. Nevertheless, predictability remains questionable. Toxic reactions to PEEK cranioplasty are unique, and long-term immunological reactions are yet to be confirmed.

The high incidence of infection with questionable evidence may have led to the underreporting of aseptic inflammation as a consequence of material-based toxicity. Aseptic inflammation as the primary cause of cranioplasty denudation and neurotoxicity are hypotheses that require clarification through animal studies involving histology and immunohistochemistry. The toxicity of different biomaterials should be compared under identical, controlled settings.

Based on the current evidence, this systematic review proposes the preferred use of CaP in younger patients thanks to its ability to integrate and grow safely with the surrounding bone. For adult patients, both titanium (alloy) and PEEK may currently be considered the safest materials to use.

Declaration of competing interest

Authors DV and DEL don't have any relevant financial relationship(s) with a commercial interest to disclose. This study is part of the PhD of DEL. The senior authors, DV and MYM, are the promotors of this PhD. MYM is innovation manager of the CADskills BV that manufactures CeTi cranioplasty".

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