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Review article

Outcomes following polyetheretherketone (PEEK) cranioplasty: Systematic review and meta-analysis

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A B S T R A C T

Polyetheretherketone (PEEK) has been used in cranioplasty since the early 2000s. However, there remains limited data that compares its long-term complication rate to autologous grafts and titanium mesh implants. To compare complication and implant failure rates after PEEK, autologous and titanium mesh cranioplasties, the authors of this study conducted a systematic review using the PubMed database. Studies that contained outcome data on complication rates of PEEK cranioplasty patients and studies that compared outcomes of patients who underwent PEEK cranioplasties versus other materials were included in the meta-analysis. Pooled odds ratios using the Mantel–Haenszel method were used for analysis. Fifteen articles, comprised of 183 PEEK cranioplasty patients were included. Of these patients, 15.3% developed post-operative complications and 8.7% experienced implant failure requiring reoperation. Patients who underwent cranioplasties with PEEK implants had 0.130 times the odds of developing post-operative complications ($P = 0.065$) and 0.574 times the odds of implant failure compared to patients with autologous bone graft cranioplasties ($P = 0.629$). Patients who had undergone PEEK cranioplasties had 0.127 times the odds of developing post-op complications ($P = 0.360$) and 0.170 times the odds of implant failure compared to individuals who had undergone titanium mesh cranioplasties ($P = 0.168$). The analysis was severely limited by the paucity in literature. However, there was a trend toward lower post-operative complication rates following PEEK cranioplasty versus autologous grafts, and lower implant failure rates with PEEK versus titanium mesh implants.

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1. Introduction

Acquired defects of the skull represent a reconstructive challenge for surgeons involved in the care of patients with full thickness cranial bone loss due to cancer, trauma, infection, or other etiologies. Early reports of cranioplasty techniques date back to the 1600s, and during the past half century this procedure has become commonplace in neurosurgical practice [1]. Autologous bone grafts of calvarial, costal, or iliac source have traditionally served as the "gold standard" in cranial vault reconstruction [2]. Bone grafts are associated with low costs and minimal risk profiles, but their use is limited by a finite amount of available donor graft material, donor site morbidity, difficulty in shaping the graft, increased operative times and perioperative risks, as well as the risks of infection, fragmentation and resorption [3].

Currently, reconstructive surgeons have an array of alloplastic materials at their disposal that serve as alternatives to autologous bone. Poly(methyl methacrylate) (PMMA) was one of the early artificial materials used to fill cranial defects. It is durable, malleable, and relatively inexpensive, but polymerizes via an exothermic reaction that can be harmful to overlying soft tissues [4]. Other clinically established bone "cements" include hydroxyapatite and calcium phosphate, each with its own set of advantages and disadvantages [5,6]. More recently, titanium mesh has become a popular material for use in cranioplasty. It is easy to handle, can be readily shaped to fit the specific contour of any given defect—either by hand or via computer-assisted design/computer-assisted manufacture (CAD/CAM) technology—and has an acceptable cost. The use of titanium alloy, however, is associated with infection, implant exposure, the generation of artifact in the setting of computed tomography (CT) or magnetic resonance imaging (MRI), and the

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potential for poor long-term adaptability with overlying soft tissue coverage [7–9].

Over the past several years, polyetheretherketone (PEEK) has gained popularity in the setting of cranial vault reconstruction [10]. PEEK has many positive qualities-it is chemically inert, the polymer maintains structural stability at temperature greater than 300 degrees Celsius, implants can be sterilized by both steam and gamma irradiation, and it has strength and elastic properties that are similar in specification to cortical bone [11–13]. It is also well suited to CAD/CAM surgical planning, rendering it adaptable to a wide array of cranial defects. Unlike titanium, it is radiolucent and does not produce significant artifacts in imaging studies [11].

Despite the increasing popularity of PEEK, there is a paucity of published data on outcomes in patients who have undergone PEEK cranioplasty. Moreover, little is known regarding how PEEK performs relative to other materials that are popularly used for cranioplasties. The authors of this study addressed this gap in knowledge by performing a meta-analysis to compare PEEK, autologous bone and titanium mesh cranioplasty outcomes. Primary outcomes of interest were implant infection, complication and failure rates (defined as implant infection or bone flap resorption requiring removal and/or replacement of implanted material) [14].

2. Methods

2.1. Search strategy and article selection

Independent searches of the currently published literature were performed by the first (M.P.) and second (L.K.C.) authors. PubMed was queried using search terms "polyetheretherketone," "PEEK," "cranioplasty," "cranial reconstruction," and "calvarial reconstruction." Titles were screened and irrelevant articles were excluded. Full-text English articles describing outcomes of PEEK cranioplasty and articles comparing outcomes of PEEK versus autologous bone or titanium mesh cranioplasties (between 2007 and 2015) were included in the meta-analysis. Case series, comparative retrospective analyses, prospective cohort studies and case reports were included. Non-English text, abstract only, articles failing to stratify outcomes based on cranioplasty technique, or previously published patient data were excluded [12,13,15–21]. The authors did not contact authors of excluded studies for further information. Bibliographies of all peer-reviewed papers generated by this query were further reviewed to identify additional articles. No registered clinical trials nor published systematic reviews/meta-analyses reporting on the use of PEEK implants in cranioplasty were identified.

2.2. Data extraction

Study sample size, patient demographics, follow-up duration indications for craniectomy, location of defect and defect size, duration of surgery and hospitalization, rates and types of complications, and implant failure rates were extracted, independently tabulated and verified by the first (M.P.) and second (L.K.C.) authors. Implant failure was defined as implant infection or bone flap resorption requiring removal and/or replacement of implanted material [14].

2.3. Statistical analysis

Statistical analysis was performed using Stata 12.1 (Stata Corp, College Station, TX, USA). The meta-analysis compared complication, failure and infection rates of PEEK versus autologous graft cranioplasties and PEEK versus titanium mesh cranioplasties using the Mantel–Haenszel method to pool data. Autologous grafts were defined as either patient-donated bone flaps that were replaced after freezing or far-site grafts harvested from patient calvarium, ribs, iliac crest [22,23]. Given the lower power of a test for heterogeneity, with only 2 studies of marginal sample sizes and poor quality, a random effects model was chosen. All analyses were tested at a 0.05 level of significance.

3. Results

A total of 23 relevant studies were identified and screened. Ultimately, 15 studies were included in the meta-analysis (Fig. 1) [3,10,11,23,22,24–33]. Two studies addressed the association between complications and failure rates in patients who underwent cranioplasty with PEEK versus autologous implants, and 2 studies addressed the same association in patients who underwent cranioplasty with PEEK versus titanium implants [23,22,28,33]. The search yielded a total of 183 patients who underwent cranioplasty repair with PEEK (Table 1). Mean age was 38.1 years and 59% ($n = 108$) of patients were male. Mean length of surgery and length-of-stay were 3.27 h and 4.46 days, respectively (Table 2). Mean follow-up was 24.1 months. Post-operative complications were reported in 28 (15.3%) of patients. The most common complications of patients undergoing cranioplasty with PEEK were infection (6%), followed by hematoma formation (2.2%) and implant exposure (1.6%). Table 3 contains an exhaustive list of all complications of published cases of patients who underwent cranioplasty with PEEK. Sixteen patients (8.7%) experienced implant failure; 10 underwent implant removal and 6 underwent removal and revision.

3.1. PEEK versus autologous bone graft

Two studies from the systematic review were included in the two meta-analyses comparing complication and failure rates of PEEK versus autologous bone graft cranioplasties. There was no significant difference in the complication rates of included and excluded studies ($P(X^2 > 2.606) = 0.106$). The pooled odds ratio (OR) of complications after PEEK cranioplasty compared to autologous graft cranioplasty was 0.130 (95% CI: 0.014, 1.138; $P = 0.065$),

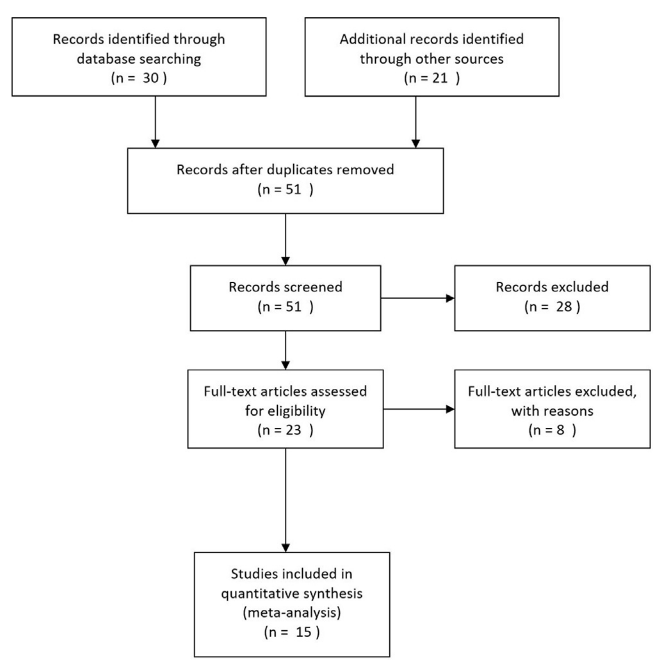

Fig. 1. Article selection.

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Table 1
Demographics data on studies meeting criteria for inclusion in systematic review.

Citation	CEBM level of evidence	Country	Materials (N)	Gender	Age (YEARS)	Follow-up (Mo)
Alonso-Rodriguez et al. 2015	4	Spain	PEEK	4M, 10F	42.7	28.6 (5–72)
Camarini et al. 2011	N/A	Brazil	PEEK	1M	47	18
Coulter et al. 2013	N/A	UK	PEEK	1F	45 yrs	12
Gilardino et al. 2015	3b	Canada	A (15); PEEK (12)	A (11M,4F); PEEK (8M, 4F)	A (10); PEEK (23.5)	12
Hanasono et al. 2009	4	US	PEEK	2M, 4F	59.8	9
Iaccarino et al. 2015	3b	Italy	A (31); HA (50); PMMA (13); PEEK (2)	A (24M, 7F); HA (35M, 15F); PMMA (8M, 5F); PEEK (1M, 1F)	-	72
Jalbert et al. 2014	4	France	PEEK	1M, 4F	49.6	-
Kim et al. 2009	4	US	PEEK	1M, 3F	19	16–20
Manrique et al. 2015	4	US	PEEK	4M, 2F	46 (±20.63)	48
Ng et al. 2014	3b	Singapore	Ti (5); Ti-AC (7); PEEK (12)	Ti (4M, 1F); Ti-AC (5M, 2F); PEEK (9M, 3F)	TI (43); Ti-AC(35); PEEK (43)	Ti (16); Ti-AC (13); PEEK (7)
O'Reilly et al. 2015	4	US	PEEK	12M, 7F	39.6 (15–81)	59 (24–106)
Rammos et al. 2015	4	US	PEEK	5M, 6F	46 (19–81)	6 (1–12)
Rosenthal et al. 2014	4	US, Israel, Singapore	PEEK	46M, 19F	35 (±14)	24 (±16)
Scolozzi et al. 2007	4	Switzerland	PEEK	1 M	42	12
Thien et al. 2014	3b	Singapore	PEEK (24); Ti (108)	PEEK (13M, 11F); Ti (72M, 36F)	PEEK (35 ± 16; Ti (43.5 ± 15.5)	PEEK (16.9 ± 14.4); Ti (43.1 ± 35.1)

A = autologous, PEEK = polyetheretherketone, HA = hydroxyapatite, PMMA = poly(methyl methacrylate), Ti = titanium, AC = acrylic, M = male, F = female.

Table 2
Summary data for patients w/PEEK cranioplasties.

Total number of patients	183
Mean follow-up, mo ($n = 176$)	24.1
Mean age, yrs ($n = 181$)	38.1
Duration of surgery, h ($n = 44$)	3.27
Length of hospitalization, days ($n = 120$)	4.46
Gender ($n = 183$)	
Male (%)	108 (59.0%)
Female (%)	76 (41.5%)
Indications for craniectomy ($n = 183$)	
Trauma (%)	99 (54.1%)
Tumor (%)	34 (34.3%)
Vascular (%)	22 (12.0%)
Congenital anomaly (%)	11 (6.0%)
Infection (%)	11 (6%)
Ischemic stroke (%)	6 (3.3%)
Location of defect ($n = 74$)	
Frontal (%)	18 (24.3%)
Parietal (%)	10 (13.5%)
Temporal (%)	9 (12.2%)
Frontoparietal (%)	8 (10.8%)
Temporoparietal (%)	6 (8.1%)
Fronto-orbital (%)	6 (8.1%)
Zygomaticomaxillary (%)	5 (6.7%)
Orbital (%)	4 (5.4%)
Orbitomaxillary (%)	2 (2.7%)
Occipitoparietal (%)	2 (2.7%)
Temporal-parietal-occipital (%)	1 (1.4%)
Parieto-occipital (%)	1 (1.4%)
Orbitofrontotemporal (%)	1 (1.4%)
Occipital (%)	1 (1.4%)

representing a 7.69-fold increase in the odds of developing post-operative complications following autologous cranioplasty compared to PEEK cranioplasty (Fig. 2). None of the 24 PEEK cranioplasties failed, while five of the 46 autologous grafts failed during the 12-month follow-up period (Fig. 3). The pooled OR of implant failure after PEEK cranioplasty compared to autologous graft cranioplasty was 0.574 (95% CI: 0.061, 5.448; $P = 0.629$), representing a 1.74-fold increase in odds of experiencing implant failure with an autologous graft.

Table 3
PEEK cranioplasty outcomes ($n = 183$).

Outcome	*N* (%)
Infection	11 (6.0)
Hematoma	4 (2.2)
Implant Exposure	3 (1.6)
Seroma	2 (1.1)
Wound Breakdown	2 (1.1)
New Seizures	2 (1.1)
CSF Leak	2 (1.1)
Post-Op Edema	2 (1.1)
Total Complication	28 (15.3)
Implant Failure	16 (8.7)

3.2. PEEK versus titanium mesh

Two studies from the systematic review were included in the two meta-analyses comparing complication and failure rates of PEEK versus titanium graft cranioplasties. There was no significant difference in the complication rates of included and excluded studies ($P(X^2 > 0.073) = 0.787$). The pooled OR of complications after PEEK cranioplasty compared to titanium cranioplasty was 0.127 (95% CI: 0.002, 8.864; $P = 0.360$), representing a 7.87-fold increase in odds of developing post-operative complications after titanium mesh cranioplasty compared to PEEK cranioplasty (Fig. 4). Three out of a total of 36 PEEK cranioplasties failed, while 33 of the 113 titanium cranioplasties failed during the follow-up period of at least 6 months (Fig. 5). The pooled OR of implant failure after PEEK cranioplasty compared to titanium cranioplasty was 0.170 (95% CI: 0.014, 2.110; $P = 0.168$). Inversely, this represents a 5.88-fold increase in odds of failure following titanium mesh cranioplasty compared to PEEK cranioplasty.

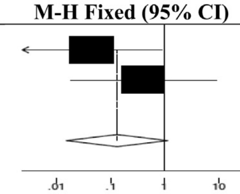
4. Discussion

Cranial reconstruction is a procedure generally performed with either autologous or alloplastic materials. An increasingly popular variation of the latter is the PEEK implant, with several advantages

Figure 2. Forest plot showing meta-analysis of 2 studies comparing complication rates with PEEK vs. autologous graft cranioplasties

	Complications			Odds Ratio
Study	**PEEK (n, %)**	**Autologous (n, %)**	**Weight**	**M-H Fixed (95% CI)**
Gilardino et al. 2015	0/12 (0%)	7/15 (46.7%)	52.14%	0.045 (0.002, 0.904)
Iaccarino et al. 2015	0/2 (0%)	10/31 (32.%)	47.86%	0.410 (0.18, 9.318)
Total (95% CI)	24	46		0.130 (0.014, 1.138)
Total events	0	17		

Odds Ratio M-H Fixed (95% CI)



Heterogeneity: Tau2=0.0204; Chi2=1.01, df=1 (P=0.315)

Test for overall effect: Z=1.84 (P=0.065)

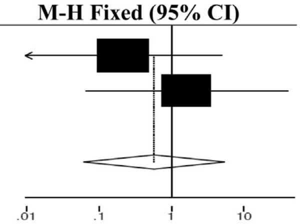
CI=confidence interval

Fig. 2. Forest plot showing meta-analysis of 2 studies comparing complication rates with PEEK vs. autologous graft cranioplasties.

Figure 3. Forest plot showing meta-analysis of 2 studies comparing failure rates with PEEK vs. autologous graft cranioplasties

	Failure			Odds Ratio
Study	**PEEK (n, %)**	**Autologous (n, %)**	**Weight**	**M-H Fixed (95% CI)**
Gilardino et al. 2015	0/12 (0%)	2/15 (13.3%)	51.58%	0.216 (0.009, 4.952)
Iaccarino et al. 2015	0/2 (0%)	3/31 (9.7%)	48.42%	1.629 (0.064, 41.290)
Total (95% CI)	14	46		0.574 (0.061, 5.448)
Total events	0	5		

Odds Ratio M-H Fixed (95% CI)



Heterogeneity: Tau2=0.000; Chi2=0.80, df=1 (P=0.372)

Test for overall effect: Z=0.48 (P=0.629)

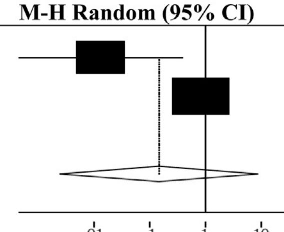
CI=confidence interval

Fig. 3. Forest plot showing meta-analysis of 2 studies comparing failure rates with PEEK vs. autologous graft cranioplasties.

Figure 4. Forest plot showing meta-analysis of 2 studies comparing complication rates with PEEK vs. titanium cranioplasties

	Complications			Odds Ratio
Study	**PEEK (n, %)**	**Titanium (n, %)**	**Weight**	**M-H Random (95% CI)**
Ng et al. 2014	0/12 (0%)	4/5 (80.0%)	42.45%	0.013 (0.0004, 0.390)
Thien et al. 2014	6/24 (25.0%)	30/108 (27.8%)	57.55%	0.867 (0.314, 2.392)
Total (95% CI)	36	113		0.127 (0.002, 8.864)
Total events	6	34		

Odds Ratio M-H Random (95% CI)



Heterogeneity: Tau2=7.32; Chi2=5.53, df=1 (P=0.019)

Test for overall effect: Z=0.92 (P=0.360)

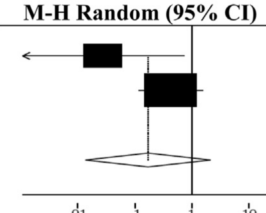
CI=confidence interval

Fig. 4. Forest plot showing meta-analysis of 2 studies comparing complication rates with PEEK vs. titanium cranioplasties.

Figure 5. Forest plot showing meta-analysis of 2 studies comparing failure rates with PEEK vs. titanium cranioplasties

	Failure			Odds Ratio
Study	**PEEK (n, %)**	**Titanium (n, %)**	**Weight**	**M-H Fixed(95% CI)**
Ng et al. 2014	0/12 (0%)	3/5 (60.0%)	34.09%	0.029 (0.001, 0.744)
Thien et al. 2014	3/24 (12.5%)	27/108 (25.0%)	65.91%	0.429 (0.118, 1.550)
Total (95% CI)	36	113		0.170 (0.014, 2.110)
Total events	3	30		

Odds Ratio M-H Random (95% CI)



Heterogeneity: Tau2=2.07; Chi2=2.30, df=1 (P=0.130)

Test for overall effect: Z=1.38 (P=0.168)

CI=confidence interval

Fig. 5. Forest plot showing meta-analysis of 2 studies comparing failure rates with PEEK vs. titanium cranioplasties.

associated with its use. Despite its increasing acceptance, however, there is a paucity of literature on the efficacy and side-effect profile of PEEK relative to other common cranioplasty techniques. To date, this is the first meta-analysis that compares outcomes of cranial vault reconstruction using PEEK, autologous bone graft, and titanium implant.

Our initial search yielded a relatively low number of available studies on outcomes of PEEK cranioplasty, and even fewer studies with comparison of PEEK to other reconstruction materials. Having said that, the literature demonstrates a steady increase in the number of publications on this topic over the past several years. While only a single case report was published in 2007, ten manuscripts were published in the past two years, including six case series and four retrospective cohorts.

A third of all studies included in our meta-analysis were carried out by institutions in the United States. Other countries represented included Singapore, Israel, France, Spain, Italy, Switzerland, Canada and Brazil. While country appears to be a strong confounder, subgroup analysis of country and outcomes was statistically infeasible. Other putative confounders such as patient population, use of antibiotics, year of procedure, time to craniectomy should be explored in future studies.

Given the dearth of literature on PEEK cranioplasty outcomes and the growing interest in the use of this material in neurosurgical and craniofacial reconstruction, our meta-analysis focused on determining how PEEK cranioplasties fare relative to other more established materials, specifically autologous bone grafts and titanium mesh implants. The authors of this study identified a 15.3% complication rate for PEEK cranioplasties, including infection, hematoma formation and implant exposure. Current literature reports comparable complication rates for cranioplasties when alternative materials are used. In fact, studies have shown a complication rate of 13.3–46.7% when autologous bone implants are used in cranioplasty and 0–58.3% when titanium mesh implants are used in cranioplasty [8,23,22,28,33–41].

Our meta-analyses did not reveal a significant difference in complication rates between PEEK and autologous bone graft or titanium graft cranioplasties. However, there was a trend toward decreased post-operative complication rates of PEEK cranioplasties compared to autologous grafts. Given that only two studies comparing outcomes were included in each of the meta-analyses, it is possible if more studies were available for inclusion, a significant difference would have been observed.

Implant infection was the most commonly observed complication among patients in this study, with 11% of the 183 patients undergoing a PEEK cranioplasty developing a post-operative infection. Reported autologous graft infection rates have ranged between 0% and 25.9% in literature, while titanium mesh implant infection rates have been reported to be lower, ranging between 0% and 11% [7,23,22,28,33,35]. Because of the small number of published studies on this topic and the limited number of patients included these studies, it was not statistically feasible to compare infection rates associated with the various materials used for cranioplasty.

Implant failure is the most serious potential adverse event associated with cranioplasty as it uniformly requires removal of the graft and reoperation using either far-site autologous grafts or synthetic material for reconstruction. Far-site autografts lead to donor-site morbidity and worse cosmetic outcomes, while synthetic materials are more costly and lead to problems with tissue compatibility [42]. In our meta-analysis, we noted a 8.7% failure rate of PEEK cranioplasties. In the current literature, reported autograft failure rates have ranged from 9.8% to 31%. Comparing these rates to those reported in our analysis, PEEK implants may fail less frequently [23,22,35]. Failure rates of titanium mesh implants have ranged from 0% to 50%, placing failure rate of PEEK cranioplasties observed in our data within the reported range [28,33,35].

We did not observe a significant difference in failure rates between either PEEK and autologous grafts or PEEK and titanium grafts in our meta-analysis. However, compared to PEEK versus autologous graft analyses, there was stronger trend toward lower failure rates of PEEK grafts compared to titanium grafts. One major difference between autologous bone and titanium mesh is variances in post-operative complications. Implant exposure was a more commonly observed complication of titanium implants than infection in the two studies that were eligible for inclusion in the pooled analysis, while infection rates were higher in autologous grafts [28,33]. Implant extrusion is a common indication for reoperation following titanium implant based cranioplasty. However, infection may be treated non-operatively in the initial period in an attempt to preserve the graft and avoid risks associated with reoperation.

4.1. Limitations

Several limitations were encountered in this study. The paucity of published studies led to a small sample size, and thus, low statistical power which could have resulted in an overestimation of the effect size. Several of the studies included in this analysis collected data in retrospective fashion, increasing the likelihood for selection and reporting biases. The follow-up period varied across studies between 6 months and almost 5 years, which may have led to an underestimation in the incidence of our outcomes of interest. Of great importance is that the authors did not adjudicate the quality of the studies examined in the meta-analysis. It was understood that the individual studies (specifically, retrospective cohorts) are predisposed to selection and publication biases; however, given the small number of studies identified further assessment of risk of bias would not have contributed significantly to the analysis. The meta-analysis predominantly consists of various pair-wise, non-randomized comparisons as opposed to examining multiple cranioplasty types, which limits interpretation of the results. Finally, given the small number of studies included in the meta-analysis, prior cranioplasty, age or location of cranioplasty, history of prior infection, and size of implant (all known factors predicting failure) could not be controlled for. Therefore, a random-effects model was chosen for the meta-analysis.

5. Conclusions

PEEK implants have been less studied in the context of their recent introduction to neurosurgical practice. The study herein presented is the first to aggregate all currently published data on outcomes of patients undergoing cranioplasty with PEEK, and to compare outcomes in patients undergoing cranioplasty with PEEK compared to autologous and titanium grafts. There was a trend toward lower post-operative complication rates after PEEK cranioplasties compared to autologous cranioplasties. Patients undergoing PEEK and titanium mesh cranioplasties, demonstrated a trend toward lower failure rates of PEEK versus titanium mesh implants. Differences in complication rates and failure rates failed to achieve statistical significance. Synthesis of the data was severely limited by the paucity of literature and low-quality of the studies analyzed. This study qualifies as a preliminary analysis that begins to address the knowledge gap in determining the complication and failure rates in cranioplasty procedures. However, future investigations involving greater numbers of comparative studies are necessary to validate the superiority of one material/technique over others.

Conflicts of interest/disclosures

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