Complications of Cranioplasty in Relation to Material: Systematic Review, Network Meta-Analysis and Meta-Regression

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BACKGROUND: Cranioplasty is a ubiquitous neurosurgical procedure consisting of reconstruction of a pre-existing calvarial defect. Many materials are available, including polymethylmethacrylate in hand-moulded (hPMMA) and prefabricated (pPMMA) form, hydroxyapatite (HA), polyetheretherketone (PEEK) and titanium (Ti).

OBJECTIVE: To perform a network meta-analysis (NMA) to assess the relationship between materials and complications of cranioplasty.

METHODS: PubMed/MEDLINE, Google Scholar, EMBASE, Scopus, and The Cochrane Library were searched from January 1, 1990 to February 14, 2021. Studies detailing rates of any of infections, implant exposure, or revision surgery were included. A frequentist NMA was performed for each complication. Risk ratios (RRs) with 95% CIs were calculated for each material pair.

RESULTS: A total of 3620 abstracts were screened and 31 full papers were included. Surgical revision was reported in 18 studies and occurred in 316/2032 cases (14%; 95% CI 11-17). PEEK had the lowest risk of re-operation with a rate of 8/157 (5%; 95% CI 0-11) in 5 studies, superior to autografts (RR 0.20; 95% CI 0.07-0.57), hPMMA (RR 0.20; 95% CI 0.07-0.60), Ti (RR 0.39; 95% CI 0.17-0.92), and pPMMA (RR 0.14; 95% CI 0.04-0.51). Revision rate was 131/684 (19%; 95% CI 13-25; 10 studies) in autografts, 61/317 (18%; 95%CI 9-28; 7 studies) in hPMMA, 84/599 (13%; 95% CI 7-19; 11 studies) in Ti, 7/59 (9%; 95% CI 1-23; 3 studies) in pPMMA, and 25/216 (12%; 95% CI 4-24; 4 studies) in HA. Infection occurred in 463/4667 (8%; 95% CI 6-11) and implant exposure in 120/1651 (6%; 95% CI 4-9).

CONCLUSION: PEEK appears to have the lowest risk of cranioplasty revision, but further research is required to determine the optimal material.

KEY WORDS: Cranioplasty, Cranial reconstruction, Decompressive craniectomy, Traumatic brain injury

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Decompressive craniectomy (DC) is a common neurosurgical procedure which may decrease mortality in cases of increased intracranial pressure (ICP) refractory to medical therapy.[1] The role of DC has also been emphasized in recent iterations of stroke management guidelines,[2,3] leading to an increased need for cranioplasty. Repair of the residual defect restores cosmesis and may also aid restoration of normal cerebrospinal fluid (CSF) hydrodynamics,[4] improvement of cerebral blood flow[5-7] and avoidance/resolution of syndrome of the trephined.[8,9]

ABBREVIATIONS: DC, decompressive craniectomy; **HA,** hydroxyapatite; **hPMMA,** hand-moulded polymethylmethacrylate; **NMA,** network meta-analysis; **NOS,** Newcastle-Ottawa Scale; **PEEK,** polyetheretherketone; **pPMMA,** prefabricated polymethylmethacrylate; **RR,** risk ratio; **TBI,** traumatic brain injury; **Ti,** titanium

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However, there is no consensus as to the optimal material. Options consist of re-use of the autogenous flap following subcutaneous preservation[10] or freezing,[11] or the use of an allograft. Traumatic brain injury (TBI) is the primary pathology in most patients undergoing DC[12] so an autograft may not always be viable. Commercially available allografts include hydroxyapatite (HA), titanium (Ti), polymethylmethacrylate (PMMA), and polyetheretherketone (PEEK), among others. Recent meta-analyses have demonstrated inferiority of autografts[12-14] but pairwise comparison has limited power to compare specific synthetic materials.

There are currently no guidelines or established best practices, though a recent consensus statement[15] has been issued and a national registry established in the United Kingdom with the development of guidelines among its goals.[16] Consequently, there is equipoise around choice of material, with significant practice variation. Here, we perform a network meta-analysis (NMA) to assess the relative risks of complications of different materials, with the aim of determining the material with the lowest propensity for complications. Specifically, our objectives were to assess the rates of infection, implant extrusion, and revision surgery across materials. An NMA is a form of meta-analysis consisting of synthesis of direct and indirect comparisons of interventions, which allows the inclusion of a larger evidence body and a more accurate comparison.[17-20] A relatively novel method of evidence synthesis, NMA has recently been incorporated in reviews attempting to differentiate between multiple interventions in the neurosurgical[21-23] and general surgical[24] literature.

METHODS

We performed a systematic review and NMA, adhering to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist[25] and PRISMA-NMA extension statement,[26] to determine the relative risk of infection, wound dehiscence/implant exposure, and need for surgical revision. No protocol for this review was published in advance.

Search Strategy

PubMed/MEDLINE, Google Scholar, EMBASE, Scopus, and The Cochrane Library were searched using the search strategy in **Supplemental Digital Content 1. Document.** Item S1. The search period was January 1, 1990 to February 14, 2021, as articles published before this time often utilized defunct materials and provided insufficient detail.

Study Selection and Data Collection

Studies reporting the rate of infection, exposure, and/or revision in at least 2 of the included materials in at least 3 patients per material arm were eligible for inclusion. Case-control, case study, and case series designs were excluded. Included materials were autologous bone, PEEK, PMMA, HA, and Ti. Nonstandard forms of included materials were also excluded, such as HA cement. Reviews, studies relating to materials not included in our analysis, studies not reporting mean follow up of at least 2 mo, and studies relating specifically to the pediatric population were excluded. Data items extracted included event rate data for each complication (infection, exposure, surgical revision) in each material, the indications for preceding DC, mean or minimum follow-up period, and demographic data including age and gender.

We considered intraoperatively hand-moulded PMMA (hPMMA) and prefabricated PMMA (pPMMA) to be distinct for our analysis given potentially significant differences.[27]

Risk of Bias Within Individual Studies

Bias was assessed at study level using the Newcastle-Ottawa Scale (NOS)[28] for cohort studies and The Cochrane RoB 2.0[29] for randomized trials.

Statistical Analysis

Statistical analysis was performed in *R v.4.0.2*[30] (The R Foundation, Vienna, Austria). Pooled estimates describing rates of each complication were calculated via the Freeman-Tukey double arcsine transformation in a random effects model using *meta*.[31]

A network was created and analyzed using *netmeta*[32] for each complication. Visual plots and tables were created using *igraph*,[33] *gemtc*,[34] and *metafor*.[35]

A frequentist model[36,37] was chosen. A node-splitting analysis[38] was performed to assess inconsistency and $P < .05$ considered significant. If inconsistency was observed, transitivity was assessed via close inspection of methodology of individual studies and demographics. Between-designs heterogeneity was quantified using a Q value and corresponding significance level, with $P < .05$ considered significant. Heterogeneity within designs was calculated via I^2 for which $I^2 > 40\%$ was considered significant. A random effects model was chosen given the well-documented heterogeneity of reported outcomes.

Network Geometry

Network plots were visually assessed for connectivity. In a network plot, each node represents a material, while connections represent direct comparisons. The thickness of the connection line relates to the volume of direct comparisons, while the size of the node is proportional to the number of cohorts in each.

Summary Measures

We calculated risk ratios (RRs) for each material pairing, incorporating direct and indirect evidence. We constructed 95% CIs for each point estimate and considered 95% CIs that did not cross 1 as significant. We also calculated a summary treatment ranking in the form of a P-score.

The P-score is distinct from the *P*-value. Its calculation can be conceptualized as representing the area under a cumulative ranking curve, where interventions with a higher P-score have a higher probability of being among the highest ranked. It is represented on a scale of 0 to 1, where 1 represents near perfect certainty that an intervention is among the highest ranked and 0 that it is among the lowest. P-scores are relative values and can be used to contrast interventions but not to assess the absolute efficacy or safety of the intervention, only its ranking among other interventions in the network.[39]

Risk of Bias Across Studies

Comparison-adjusted funnel plots[40] were generated, and Egger's test[41] performed for each analysis. Plots were visually inspected for bias and Egger's $P < .05$ was taken as statistically significant.

Additional Analyses

Meta-regression evaluating the effect of moderators on pooled estimates for rate of infection, exposure, and revision was performed using *metafor*.[35] Moderators included indication for DC, sex, age, and study quality. Studies reporting incomplete demographic data were excluded.

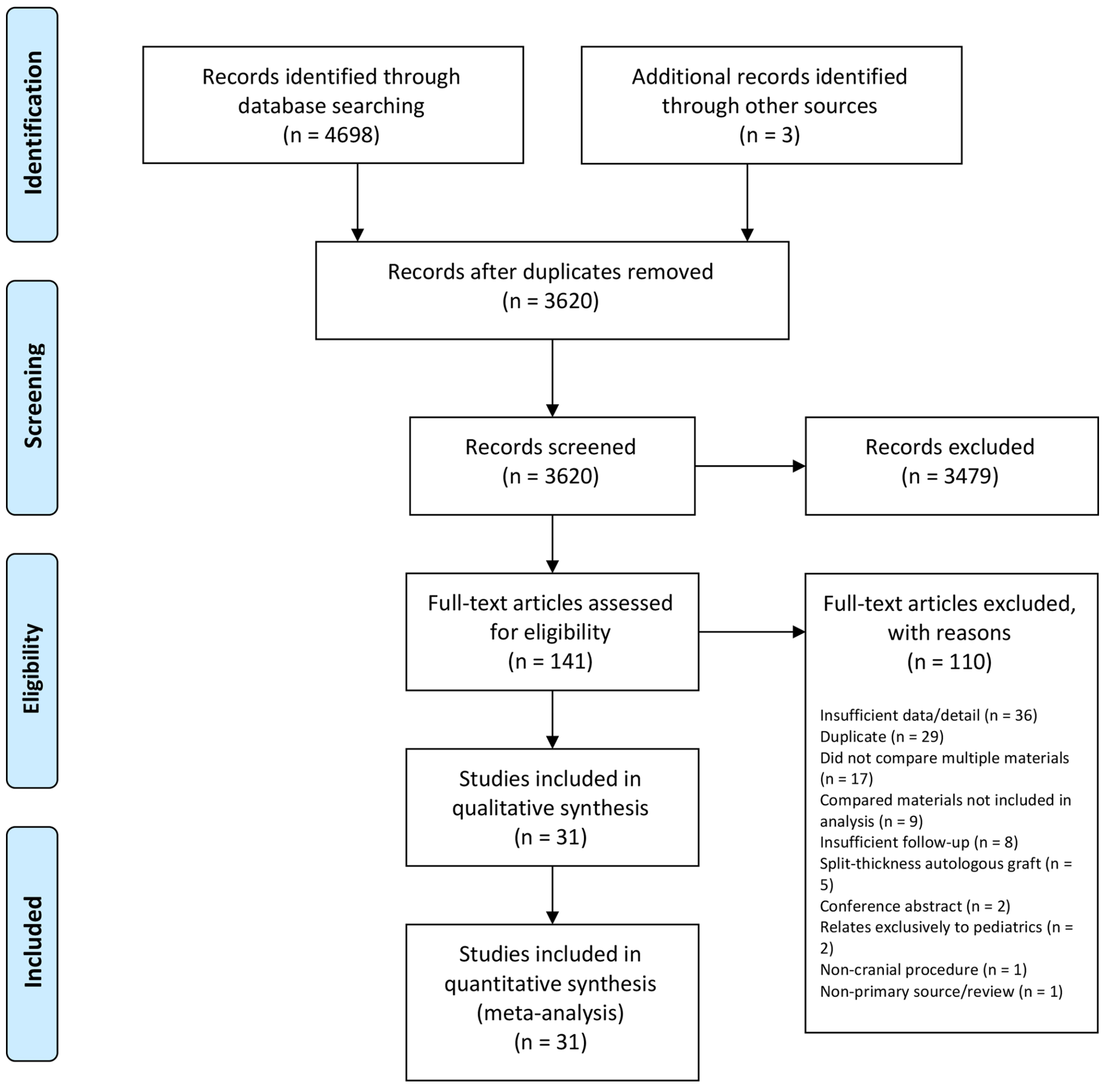


FIGURE 1. *PRISMA flowchart depicting article screening and selection.*

Correlation among moderator variables was investigated via calculation of crude correlation coefficient (*r*). Multiple meta-regression was performed using the maximum likelihood method with Knapp-Hartung adjustment.

RESULTS

The initial search yielded 4701 results. A total of 3620 abstracts were screened, and 141 full papers were assessed. A total of 31 papers were included (Figure 1). Characteristics of the studies are provided in Table 1.

Summary information for each analysis, including distribution of cohorts and studies, is provided in **Supplemental Digital Content 2. Document, Table S1**. Individual study results and effect sizes for each analysis are provided in **Supplemental Digital Content 3. Document, Table S2**. Descriptive statistics are provided in Table 2. The influence of the individual studies and full results of the meta-analysis from which these are derived is shown in **Supplemental Digital Content 6. Figure, Figure S1**.

Summary of demographic data is provided in Table 3 and study level in **Supplemental Digital Content 4. Document, Table S3**. The proportion of direct and indirect evidence incorporated is shown for infections (**Supplemental Digital Content 7. Figure, Figure S2A**), exposures (**Supplemental Digital Content 7. Figure, Figure S2B**), and revision surgery (**Supplemental Digital Content 7. Figure, Figure S2C**).

TABLE 1. **Characteristics of the Included Studies**

Study	Design	Materials	n	Follow up (mo)	Location	ROB	Inf.	Exp.	Rev.
Asaad 2021[75]	Retrospective cohort	PEEK, Ti	77	50 (PEEK) 32 (Ti)	United States	8	Y	Y	Y
Sahoo 2021[76]	Retrospective cohort	A, pPMMA, Ti	158	>6	India	4	Y	N	Y
Ganau 2020[55]	Retrospective cohort	HA, hPMMA	181	41	France	7	Y	N	Y
Hambock 2020[77]	Retrospective cohort	A, hPMMA	156	10.8 (A) 4.8 (hPMMA)	Austria	5	Y	N	Y
Kim 2019[78]	Retrospective cohort	A, Ti	44	>12	South Korea	5	N	Y	N
Vince 2019[79]	Retrospective cohort	A, hPMMA	286	15.2 (A) 22.2 (PMMA)	Germany	6	N	N	Y
Yeap 2019[45]	Retrospective cohort	A, Ti, pPMMA	596	42.9	Taiwan	8	Y	Y	N
Honeybul 2017[80,81]	Randomized trial	A, Ti	64	>24	Australia	Low[a]	Y$^{\sim}$	N	Y
Kim 2018[82]	Retrospective cohort	A, Ti	76	28.8 (A) 26.3 (Ti)	South Korea	7	Y	N	N
Kwiecien 2018[69]	Retrospective cohort	A, Ti	165	47	United States	8	Y	Y	Y
Moles 2018[83]	Retrospective cohort	A, HA	92	24	France	6	Y	N	Y
Zhang 2018[84]	Retrospective cohort	PEEK, Ti	185	13.5 (PEEK) 14.2 (Ti)	China	6	Y	Y	Y
Kim 2017[85]	Retrospective cohort	A, hPMMA	127	15	South Korea	6	Y	Y	N
Honeybul 2016[86]	Retrospective cohort	A, Ti	512	>6	Australia	5	Y	N	N
Kimchi 2016[87]	Retrospective cohort	A, pPMMA	61	20.5	Israel	8	Y	N	N
Mohamad 2016[88]	Retrospective cohort	A, hPMMA	172	>2	Malaysia	5	Y	N	N
Morton 2016[89]	Retrospective cohort	A, PEEK	646	7.9	United States	7	Y	N	N
Zegers 2017[90]	Retrospective cohort	PEEK, Ti	25	56.6	Netherlands	5	N	Y	Y
Iaccarino 2015[91]	Prospective cohort	A, HA, pPMMA, PEEK[b]	94	11	Italy	7	Y	N	Y
Lindner 2016[92]	Randomized trial	Ti, HA	50	6	Germany	SC[a]	Y	N	Y
Piitulainen 2015[93]	Retrospective cohort	A, Ti, hPMMA	40	36	Finland	6	N	N	Y
Thien 2015[94]	Retrospective cohort	PEEK, Ti	132	16.9 (PEEK) 43.1 (Ti)	Singapore	6	Y	Y	Y
Klinger 2014[95]	Retrospective cohort	A, pPMMA	258	16	United States	7	Y	N	N
Ng 2014[96]	Retrospective cohort	PEEK, Ti	24	11	Singapore	6	N	Y	Y
Lee 2013[57]	Retrospective cohort	PEEK, Ti	228	>12	Singapore	6	Y	Y	N
Al-Tamimi 2012[97]	Prospective cohort	Ti, hPMMA	126	97.2 (PMMA) 34 (Ti)	United Kingdom	7	N	N	Y
Lee 2012[98]	Retrospective cohort	A, hPMMA	133	18	South Korea	6	Y	N	N
Lee 2009[72]	Retrospective cohort	A, hPMMA, pPMMA	131	>6	Taiwan	6	N	N	Y
Kriegel 2007[99]	Retrospective cohort	A, hPMMA	48	44	Germany	5	Y	Y	Y
Matsuno 2006[46]	Retrospective cohort	A, hPMMA, pPMMA, Ti	189	64	Japan	7	Y	N	N
Moreira-Gonzalez 2003[59]	Retrospective cohort	A, hPMMA	269	39.6	United States	7	Y	N	N
Total			5345				24	11	18

Columns indicate whether a given complication from each study was included in the analysis. Follow-up period denoted refers to the mean follow-up period in months unless otherwise stated. Risk of bias was assessed using the Newcastle-Ottawa Scale except where otherwise stated. Sample size refers to the number of patients in the study in which the included material(s) were used.

Y = yes, N = no, HA = hydroxyapatite, PMMA = polymethylmethacrylate, A = autologous bone, Ti = titanium, PEEK = polyetheretherketone, ROB = study quality/risk of bias assessed via Newcastle-Ottawa Scale, Inf. = infections, Exp. = implant exposure/wound dehiscence, Rev. = revision surgery, n = sample size, SC = some concerns.

[a] Assessed via Cochrane risk of bias tool 2.0 (otherwise assessed as Newcastle-Ottawa score).

[b] The PEEK arm of this study (n = 2) was excluded.

Infection

A total of 463 infections were reported in 4667 patients (8%; 95% CI 6-11) across 24/31 studies (77.4%). A node-splitting analysis revealed no significant inconsistency (Q = 13.15, *P* = .22) (**Supplemental Digital Content 8. Figure, Figure S3**). However, there was significant within-designs heterogeneity in this analysis ($I^2 = 68.9\%$). Figure 2A depicts the network, with no studies reporting the relationship between PEEK vs pPMMA, hPMMA, or HA.

HA had the lowest propensity for infection (P-score = 0.85) with a pooled infection rate of 13/216 (6%; 95% CI 2-11; 4 studies). Ti had a similarly low rate of infection of 99/1101

TABLE 2. The Rates of Infection, Implant Exposure Injury, and Revision

	Infection				Exposures				Revision			
Material	**N**	**% (95% CI)**	**I^2**	**S**	**N**	**% (95% CI)**	**I^2**	**S**	**N**	**% (95% CI)**	**I^2**	**S**
hPMMA	54/443	12% (4-23)	87%	8	3/128	2% (0-10)	59%	2	61/317	18% (9-28)	75%	7
pPMMA	74/347	12% (0-32)	93%	6	10/139	7% (3-12)	N/A[b]	1	7/59	9% (1-23)	44%	3
PEEK	18/289	5% (2-9)	20%	5	7/167	3% (0-8)	20%	6	8/157	5% (0-11)	45%	5
HA	13/216	6% (2-11)	38%	4	*N/A*[a]				25/216	12% (4-24)	78%	4
Ti	99/1101	8% (5-12)	77%	12	75/742	11% (6-17)	75%	9	84/599	13% (7-19)	73%	11
Autologous	205/2271	8% (5-10)	71%	18	25/475	3% (1-7)	34%	5	131/684	19% (13-25)	73%	10
Total	463/4667	8% (6-11)	81%	24	120/1651	6% (4-9)	66%	11	316/2032	14% (11-17)	74%	18

N refers to the raw number of events per total patients (events/patients) for each material. Percentage rate of complications (%) is derived from a random effects model meta-analysis of proportions, with the associated 95% confidence interval (95% CI) also provided. I^2 refers to the heterogeneity observed in each material subgroup, and S refers to the number of studies included in each analysis.

N = raw no of events, % = pooled proportion, 95% CI = 95% confidence interval, I^2 = heterogeneity, S = number of studies from which the estimate is derived.

[a] No data for this material.

[b] Heterogeneity not estimable as only a single study was available.

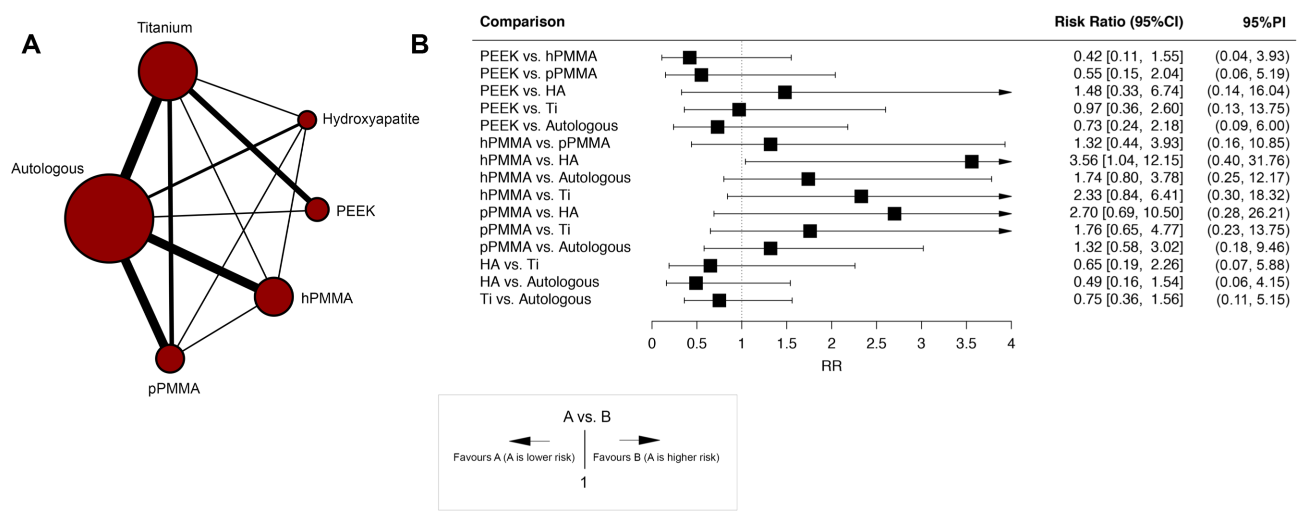


FIGURE 2. *The infections analysis. In the network plot* **A**, *each ellipse (node) represents a specific material, with its size proportional to the number of cohorts in the node. Connections between nodes represent direct comparative studies between materials, with the weight of the connecting lines representing the volume of direct comparative evidence.* **B**, *Forest plot depicting the estimated risk ratio (RR) for each material pair denoted by the black square, and its associated 95% CI denoted by the width of the line, with a higher RR indicating a higher risk in the material on the left side of the "vs." The 95% PI refers to the 95% prediction interval for each point estimate.*

(8%; 95% CI 5-12; 12 studies), ranking second in the NMA (P-score = 0.67). PEEK ranked third (P-score = 0.65) with a pooled rate of 18/289 (5%; 95% CI 2-9; 5 studies). Autologous bone had an infection rate of 205/2271 (8%; 95% CI 5-10; 18 studies), ranking fourth (P-score = 0.46). There were 74/347 infections (12%; 95% CI 0-32; 6 studies) in pPMMA, ranking fifth (P-score = 0.27). hPMMA was noticeably inferior to other materials (P-score = 0.11), ranking last in the NMA with an infection rate of 54/443 (12%; 95% CI 4-23; 8 studies), which was significantly higher than HA (RR 3.56; 95% CI 1.04-12.15).

However, no material demonstrated categorical superiority and no other point estimates were statistically significant (Figure 2B).

Implant Exposure

A total of 120 incidences of wound complications were reported in 1651 patients (6%; 95% CI 4-9) across 11/31 studies (35.5%). There was insignificant inconsistency (Q = 1.31, *P* = .25) (**Supplemental Digital Content 9. Figure, Figure S4**). HA was excluded as no studies reported the rate of exposure. There was no within-designs heterogeneity ($I^2 = 0\%$).

TABLE 3. Summary Statistics of Demographics in Included Studies

Demographics	N (%)
Age (mean in years)	43.5
Male	3646 (65.9%)
Female	1887 (34.1%)
Indication for DC	**N (%)**
TBI	2556 (51.3%)
Neurovascular	1436 (28.8%)
Other	987 (19.9%)

Figure 3A depicts the network. hPMMA was compared only to autologous bone, PEEK was compared only to Ti and autologous, and Ti was not directly compared to hPMMA.

Ti had the highest propensity for wound dehiscence and implant exposure, ranking lowest in the NMA (P-score = 0.02) with a rate of 75/742 (11%; 95% CI 6-17; 9 studies). hPMMA ranked highest (P-score = 0.78) with 3/128 incidences (2%; 95% CI 0-10; 2 studies). Autologous ranked second (P-score = 0.64) with a rate of 25/475 (3%; 95% CI 1-7; 5 studies). PEEK ranked third (P-score = 0.56) with a rate of 7/167 (3%; 95% CI 0-8; 6 studies). Only one study assessed pPMMA, reporting a rate of 10/139 (7%; 95% CI 3-12), ranking fourth (P-score = 0.50).

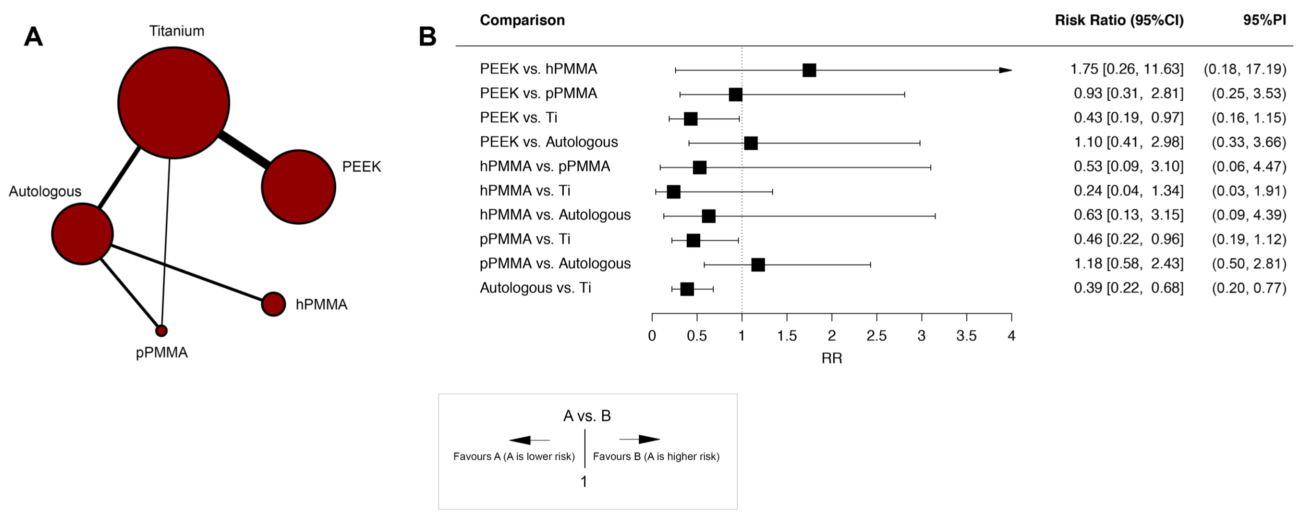
PEEK had a significantly lower risk of implant exposure than Ti (RR 0.43; 95% CI 0.19-0.97), as did pPMMA (RR 0.46; 95% CI 0.22-0.96) and autologous bone (RR 0.39; 95% CI 0.22-0.68). No other point estimates reached significance (Figure 3B).

Revision

A total of 316 revisions were reported in 2032 patients (14%; 95% CI 11-17) across 18/31 studies (58.1%). There was no significant inconsistency (Q = 11.45, $P = .32$) (**Supplemental Digital Content 10. Figure, Figure S5**) and insignificant within-designs heterogeneity ($I^2 = 27.5\%$). The network is depicted in Figure 4A and point estimates in Figure 4B. PEEK was compared directly only to Ti. HA was not compared directly to hPMMA and pPMMA was not compared directly to Ti.

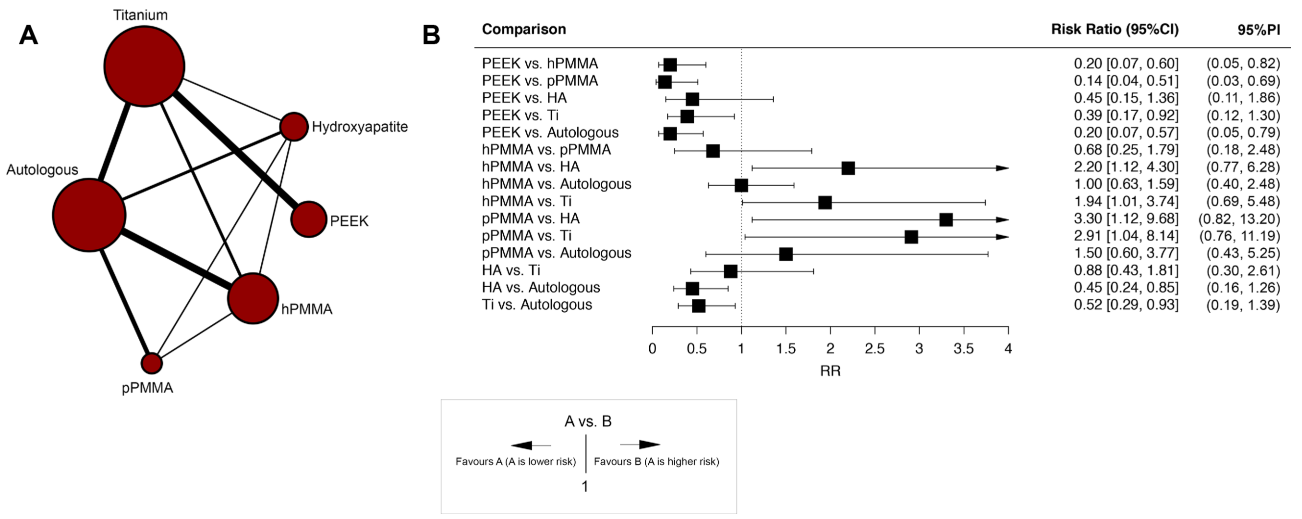
PEEK ranked highest in the NMA (P-score = 0.98) with a revision rate of 8/157 (5%; 95% CI 0-11; 5 studies) (Figure 5). HA ranked second (P-score = 0.74) with an incidence of 25/216 (12%; 95% CI 4-24; 4 studies), followed by Ti (P-score = 0.66) with 84/599 (13%; 95% CI 7-19; 11 studies). hPMMA had a rate of 61/317 (18%; 95% CI 9-28; 7 studies), ranking fourth (P-score = 0.27). hPMMA was equivalent to autologous (P-score = 0.27), which had a rate of 131/684 (19%; 95% CI 13-25; 10 studies). pPMMA ranked lowest (P-score = 0.09) with a revision rate of 7/59 (9%; 95% CI 1-23; 3 studies).

PEEK had a significantly lower risk than hPMMA (RR 0.20; 95% CI 0.07-0.60), Ti (RR 0.39; 95% CI 0.17-0.92), autologous bone (RR 0.20; 95% CI 0.07-0.57), and pPMMA (RR 0.14; 95% CI 0.04-0.51). hPMMA had a significantly higher risk than HA (RR 2.20; 95% CI 1.12-4.30) and Ti (RR 1.94; 95%CI 1.01-3.74). pPMMA had also a significantly higher risk than HA (RR 3.30; 95% CI 1.12-9.68) and Ti (RR 2.91; 95% CI 1.04-8.14). Compared to autologous bone, both HA (RR 0.45; 95% CI 0.24-0.85) and Ti (RR 0.52; 95% CI 0.29-0.93) were superior.



Comparison	Risk Ratio (95%CI)	95%PI
PEEK vs. hPMMA	1.75 [0.26, 11.63]	(0.18, 17.19)
PEEK vs. pPMMA	0.93 [0.31, 2.81]	(0.25, 3.53)
PEEK vs. Ti	0.43 [0.19, 0.97]	(0.16, 1.15)
PEEK vs. Autologous	1.10 [0.41, 2.98]	(0.33, 3.66)
hPMMA vs. pPMMA	0.53 [0.09, 3.10]	(0.06, 4.47)
hPMMA vs. Ti	0.24 [0.04, 1.34]	(0.03, 1.91)
hPMMA vs. Autologous	0.63 [0.13, 3.15]	(0.09, 4.39)
pPMMA vs. Ti	0.46 [0.22, 0.96]	(0.19, 1.12)
pPMMA vs. Autologous	1.18 [0.58, 2.43]	(0.50, 2.81)
Autologous vs. Ti	0.39 [0.22, 0.68]	(0.20, 0.77)

FIGURE 3. *The implant exposure injuries analysis. In the network plot* **A**, *each ellipse (node) represents a specific material, with its size proportional to the number of cohorts in the node. Connections between nodes represent direct comparative studies between materials, with the weight of the connecting lines representing the volume of direct comparative evidence.* **B**, *Forest plot depicting the estimated risk ratio (RR) for each material pair denoted by the black square, and its associated 95% CI denoted by the width of the line, with a higher RR indicating a higher risk in the material on the left side of the "vs." The 95% PI refers to the 95% prediction interval for each point estimate.*



Comparison	Risk Ratio (95%CI)	95%PI
PEEK vs. hPMMA	0.20 [0.07, 0.60]	(0.05, 0.82)
PEEK vs. pPMMA	0.14 [0.04, 0.51]	(0.03, 0.69)
PEEK vs. HA	0.45 [0.15, 1.36]	(0.11, 1.86)
PEEK vs. Ti	0.39 [0.17, 0.92]	(0.12, 1.30)
PEEK vs. Autologous	0.20 [0.07, 0.57]	(0.05, 0.79)
hPMMA vs. pPMMA	0.68 [0.25, 1.79]	(0.18, 2.48)
hPMMA vs. HA	2.20 [1.12, 4.30]	(0.77, 6.28)
hPMMA vs. Autologous	1.00 [0.63, 1.59]	(0.40, 2.48)
hPMMA vs. Ti	1.94 [1.01, 3.74]	(0.69, 5.48)
pPMMA vs. HA	3.30 [1.12, 9.68]	(0.82, 13.20)
pPMMA vs. Ti	2.91 [1.04, 8.14]	(0.76, 11.19)
pPMMA vs. Autologous	1.50 [0.60, 3.77]	(0.43, 5.25)
HA vs. Ti	0.88 [0.43, 1.81]	(0.30, 2.61)
HA vs. Autologous	0.45 [0.24, 0.85]	(0.16, 1.26)
Ti vs. Autologous	0.52 [0.29, 0.93]	(0.19, 1.39)

FIGURE 4. *The revisions analysis. In the network plot* **A**, *each ellipse (node) represents a specific material, with its size proportional to the number of cohorts in the node. Connections between nodes represent direct comparative studies between materials, with the weight of the connecting lines representing the volume of direct comparative evidence.* **B**, *Forest plot depicting the estimated risk ratio (RR) for each material pair denoted by the black square, and its associated 95% CI denoted by the width of the line, with a higher RR indicating a higher risk in the material on the left side of the "vs." The 95% PI refers to the 95% prediction interval for each point estimate.*

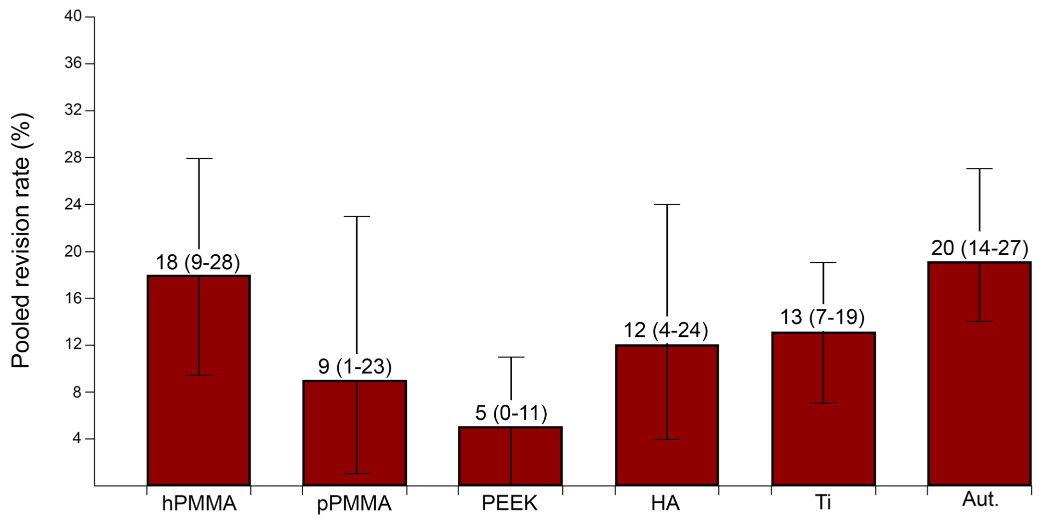


FIGURE 5. *Histogram depicting the rate of revision surgery in each material. The numbers associated with each bar represent the pooled estimate of revision rate derived from the random-effects meta-analysis of proportions with its associated 95% CI in parentheses. The error bars displayed for each bar also refer to the 95% CI. "Aut." refers to autologous bone.*

Meta-regression

Relationships between moderator variables are depicted in **Supplemental Digital Content 11. Figure, Figure S6** and the results in Table 4. Seven studies were excluded (**Supplemental Digital Content 4. Document, Table S3**). None of the meta-regression models or individual moderators appeared to be significant (Table 4).

Risk of Bias Across Studies

Funnel plots are provided in **Supplemental Digital Content 12. Figure, Figure S7**. There was some visual asymmetry in all analyses, suggesting small-study effects. However, Egger's test did not reach statistical significance for any of infections ($P = .69$), exposures ($P = .90$), or revisions ($P = .21$).

TABLE 4. Results of Meta-regression Evaluating the Effect of Moderator Variables on Outcomes in Each Analysis

Variable	Infection (n = 19) *P* value	Exposure (n = 8) *P* value	Revision (n = 13) *P* value
NOS	.442	.960	.306
Trauma	.380	.709	.863
Neurovascular	.562	.448	.455
Age	.708	.680	.393
Male	.282	.143	.741
Overall	.677 ($R^2 = 13.5\%$)	.075 ($R^2 = 85.0\%$)	.600 ($R^2 = 30.1\%$)

Following the exclusion of studies reporting insufficient demographic information, 19 studies were assessed in the infections analysis, 8 in the exposure injury analysis and 13 in the revisions analysis. The prospectively determined *P*-value is provided, with $P < .05$ considered evidence of a significant influence. "Overall" refers to the influence of a multiple meta-regression model incorporating all moderator variables. R^2 refers to the proportion of heterogeneity accounted for by the moderator variables.
NOS = study quality assessed using the Newcastle-Ottawa Scale.

TABLE 5. P-Score League Table per Analysis

	Infections		Exposure		Revision	
Rank	**Material**	**P-score**	**Material**	**P-score**	**Material**	**P-score**
1.	HA	0.85	hPMMA	0.78	PEEK	0.98
2.	Ti	0.67	Autologous	0.64	HA	0.74
3.	PEEK	0.65	PEEK	0.56	Ti	0.66
4.	Autologous	0.46	pPMMA	0.50	hPMMA	0.27
5.	pPMMA	0.27	Ti	0.02	Autologous	0.27
6.	hPMMA	0.11	*HA*	N/A[a]	pPMMA	0.09

The P-score represents the probability that a material is among the highest ranked on a scale of 0 to 1, with a P-score of 1 representing near certainty that a given treatment is among the highest ranked, and a P-score of zero representing near certainty that a treatment is among the lowest ranked.
[a] HA was excluded from the exposures analysis as no direct comparative data were available.

Summary

A summary of rankings by P-score is provided in Table 5, while a league table summary of RRs is shown in **Supplemental Digital Content 5. Document, Table S4**.

DISCUSSION

Infection

Infection was the most consistently reported complication. Our rate of 8% is similar to previous analyses, which have shown rates of 5.9% to 8.6%.[12,42-44] Late infection is well described,[45-48] documented up to 20 yr later.[48] Therefore, estimating the true infective burden is difficult. HA appeared to have the lowest risk of infection in our analysis, but this was significantly superior only to hPMMA. Ours included only 216, but an analysis of 1549 HA cranioplasties demonstrated a lower infection rate of 2.05%.[49] This low rate may be secondary to improved osseoconductivity[50-52] though more longitudinal follow-up data are needed to quantify this effect. Confidence intervals for point estimates of HA were wide in all analyses as due to low sample sizes and high variance. HA demonstrates a promising low infection risk with potential additional benefit, but requires further investigation in direct comparison to other materials.

hPMMA appeared to have the highest risk of infection, with pPMMA also having a relatively high risk. There is significant variation in published rates of infection in PMMA, with reports from 7.4% to 45%.[45,53-55] It has been suggested that this high infection rate is a consequence of poor osseoinduction[56] or of a lobular morphology.[46] However, this analysis demonstrated significant heterogeneity ($I^2 = 68.9\%$) and, like previous reviews,[12-14] we found that there was no concrete association between material and risk of infection.

Wound Dehiscence and Implant Exposure

Ti was strongly associated with the highest rate of wound complications (10%; 95% CI 6-17; P-score = 0.02), while other materials were approximately equivalent, which is consistent with the findings of a previous meta-analysis.[14] Implant exposure is often associated with infection requiring revision.[57] Ti-associated implant exposure has been reported to occur as a result of an inflammatory process rather than a wound complication[58-61] and patients with evidence of metal hypersensitivity have a higher rate of Ti cranioplasty failure.[61] Implant exposure in Ti is often topographically unrelated to the incision, while in autologous bone this is primarily a result of mechanical skin erosion by fixation hardware.[45] Its prevalence is also potentially underestimated in the literature, as scalp atrophy may worsen persistently beyond a period of 10 yr unlike other materials,[60] so this may present beyond the follow-up period of most studies.

We considered wound dehiscence and implant exposure as a single cohort, as this often exists as a continuum and most studies did not provide adequate detail to separate the two. No data were available for HA. However, we would expect a very low rate of implant exposure in HA as in non-Ti implants this seems to be caused by metal fixation hardware,[45] whereas HA implants are typically sutured into place.

Revision

PEEK appeared to have the lowest risk of revision (5%; 95% CI 0-11; P-score = 0.98), which was superior to all other materials except HA. Previous reviews have demonstrated an association between autografts and surgical revision[12-14] when compared to aggregated allografts, with one also showing an advantage to HA and Ti specifically over autologous bone, and also PEEK over Ti.[14] Our findings are largely consistent with these, but additionally demonstrate an advantage for HA and Ti over other alloplastic materials, and an apparent equivalence of PMMA and autologous bone.

In PMMA, this higher risk may be the result of the higher rate of infection we observed. Aseptic bone resorption may be the etiology of excess re-operation in autologous bone. Resorption is a common phenomenon, with reported rates ranging from 4.1% to 35.1%.[62-65] This complication is unique to autologous bone[56,66] and was therefore not specifically assessed in our analysis. Despite the upfront higher cost of allografts, increased revision rate results in a similar or higher cost of autografts.[67,68] The advantage to PEEK over Ti may be a product of the increased rate of exposure in Ti implants, a complication that usually requires extensive revision.[57,60,69]

Limitations

There are several limitations to this study. Most prominently, the majority of available literature is of low quality, with poor adherence to reporting guidelines and heterogeneous, incomplete definitions of complications. Most studies (27/31; 87%) are retrospective cohort designs making residual confounding likely. Publication bias is likely to be present given the evidence base consisting of relatively small studies. These issues are reflected in the large range of reported rates for each complication.

In addition, there was substantial variation in indication for DC and demographics across studies (**Supplemental Digital Content 4. Document, Table S3**), which can potentially violate the transitivity assumption of the NMA though no inconsistency was demonstrated. We considered Ti mesh implants equivalent to Ti plate implants which are arguably distinct. Timing may have an effect[70] which we did not assess and included studies varied in this regard. Follow-up periods and sample sizes also differed. Distribution of evidence was unbalanced, with a large number of studies assessing autologous bone (n = 22) and comparatively fewer assessing newer alloplastic materials such as PEEK (n = 7) and HA (n = 4). Many studies compared autografts to a single allograft, and cohorts may be disseminated in time which can be confounding. Studies also had a wide geographic distribution (Table 1), and there is consequently significant risk of center effects.

Lastly, we did not consider cosmesis. Poor cosmesis is a common complication,[71] but is only sporadically assessed.[72-74] It is likely that cosmesis is related to material[56,66] so a comprehensive assessment of materials should consider this.

CONCLUSION

Cranioplasty has a relatively high infection rate of 8% and approximately 14% of cranioplasties require re-operation. PEEK appears to have the lowest risk of revision surgery, followed by HA and Ti. PEEK, HA, and Ti appear to be superior to autologous bone and PMMA. HA appears to have the lowest risk of infection and may have further additional benefits in terms of cosmesis and long-term osseoinduction, which we did not assess. Ti had reasonable performance but was associated with a high rate of implant exposure. PEEK, HA, and Ti all appear to have a lower risk of revision than autografts and PMMA.

However, the power of our analysis was limited by low quality of the literature, the presence of significant confounding, and small sample sizes examining newer allografts. Therefore, no conclusive benefit to any specific material is apparent. Furthermore, cosmesis was not assessed. Therefore, further research is necessary to elucidate the clinical outcomes in newer-generation allografts, along with a patient-centered assessment of cosmesis and the optimal material for achieving it.

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Supplemental Digital Content 1. Document. Item S1. Search queries are detailed below. Searches were updated sequentially via re-running at interim dates until February 14, 2021. Citations were deduplicated via fuzzy logic matching using revtools in R v4.0.2. Abstracts were screened using Rayyan QCRI by two authors (J.H., J.T.). Full papers collated in spreadsheets and data extracted. During abstract screening, systematic reviews were flagged and the bibliographies were hand-screened for any additional potentially relevant references, which resulted in the additional inclusion of 3 additional citations for assessment.

Supplemental Digital Content 2. Document. Table S1. Number of cohorts and distribution of studies per number of arms for each analysis.

Supplemental Digital Content 3. Document. Table S2. Data extracted including events, sample sizes, and fitted risk ratios for each study included in each analysis.

Supplemental Digital Content 4. Document. Table S3. Study-level demographic and indication data extracted.

Supplemental Digital Content 5. Document. Table S4. League table depicting all direct comparison risk ratios (RRs) for each analysis. The upper triangle depicts direct estimates attained by conventional pairwise meta-analysis, while the lower triangle contains the network model estimates. Estimates are presented in the format RR (95%CI).

Supplemental Digital Content 6. Figure. Figure S1. Results of the meta-analysis of proportions showing the pooled rate of infection, implant exposure injury, and revision. **A**, Relates to the infections analysis, **B**, to the exposure injury analysis, and **C**, to the revision analysis.

Supplemental Digital Content 7. Figure. Figure S2. Plot depicting the direct evidence proportion for each estimate in each network. Bars relate to the proportion of the pooled network estimate for each material derived from direct estimates via conventional meta-analysis (orange) and indirect evidence (blue). **A**, Relates to the infections analysis, **B**, to the exposures analysis, and **C**, to the revisions analysis.

Supplemental Digital Content 8. Figure. Figure S3. Node-splitting analysis of inconsistency for the infections analysis. In the node-splitting analysis, the results of direct estimates derived from conventional pairwise meta-analysis are compared to the indirect estimates derived from the network for each pair. A *P*-value (direct evidence column) of <.05 suggests significant incongruence between the direct and indirect estimates, which is suggestive of the presence of inconsistency in the network. In this case, no significant inconsistency was observed.

Supplemental Digital Content 9. Figure. Figure S4. Node-splitting analysis of inconsistency for the implant exposure injuries analysis. In the node-splitting analysis, the results of direct estimates derived from conventional pairwise meta-analysis are compared to the indirect estimates derived from the network for each pair. A *P*-value (direct evidence column) of < .05 suggests significant incongruence between the direct and indirect estimates, which is suggestive of the presence of inconsistency in the network. In this case, no significant inconsistency was observed but assessment was limited by the fact that direct evidence was available for only two material pairs.

Supplemental Digital Content 10. Figure. Figure S5. Node-splitting analysis of inconsistency for the revisions analysis. In the node-splitting analysis, the results of direct estimates derived from conventional pairwise meta-analysis are compared to the indirect estimates derived from the network for each pair. A *P*-value (direct evidence column) of < .05 suggests significant incongruence between the direct and indirect estimates, which is suggestive of the presence of inconsistency in the network. In this case, no significant inconsistency was observed.

Supplemental Digital Content 11. Figure. Figure S6. Correlation plot displaying the inter-relationship between moderator variables. In the correlation plot, the top right triangle displays the correlation coefficient the intersecting variables. The bottom left triangle displays a scatter plot between the two variables. **A**, Refers to infection, **B**, to implant exposure injuries, and **C**, to revision. Traumatic brain injury as an indication for DC was correlated with proportion of male patients, in keeping with the male predominance for TBI. Males and females were perfectly proportional, so only male patients were included in regression as a surrogate for the effect of sex. NOS = Newcastle-Ottawa Scale, nv = neurovascular.

Supplemental Digital Content 12. Figure. Figure S7. Comparison-adjusted funnel plots assessing the influence of small study effects on the P-score ranking for each analysis. The order of treatments chosen for each hypothesis test was determined by the P-score ranking table for each analysis. The results of linear regression (Egger's test) to assess the significance of the relationship are provided in the top left corner of each plot. **A**, Relates to the infections analysis, **B**, to the exposures analysis, and **C**, to the revisions analysis.

COMMENT

The authors performed a sophisticated review and network meta-analysis on complications of cranioplasty. Studies eligible for inclusion required to investigate at least two different cranioplasty materials among autologous bone, hydroxyapatite, titanium, polymethylmethacrylate (PMMA) and polyetheretherketone (PEEK). Rates of infection, implant exposure and/or need for revision surgery were compared. Appropriately addressed by the authors, the study's limitations need careful consideration when interpreting the results. Most included studies are retrospective cohort studies with appreciable inherent risk for confounding. Due to current lack of guidelines, inter-institutional differences – and depending on treatment era even intra-institutional differences – likely affect outcome. Different periprocedural (prophylactic) antibiotic regimens, different timing between craniectomy and cranioplasty, and different preferences for indicating a re-cranioplasty after a previous complication requiring revision potentially influence complication rates. Moreover, the included studies' follow-up differed substantially, thereby potentially distorting endpoint analysis. Nevertheless, the authors' study provides a strong synopsis on rates of infection, implant exposure and/or need for revision surgery. Since cranioplasty represents a common neurosurgical procedure, its comparatively high-complication profile requires appreciation by each neurosurgeon. While this study does not provide a foundation in favor of or against specific implant materials, it definitely exhibits that further investigation of appropriate material selection for cranioplasty is indispensable.

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