

# Comparison of autograft and implant cranioplasty in pediatrics: A meta-analysis

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Original Article

# Comparison of autograft and implant cranioplasty in pediatrics: A meta-analysis

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## ABSTRACT

**Background:** Cranioplasty in pediatrics is quite challenging and intricate. The ideal material for it is still debatable until now due to the limited study comparing autologous and implant grafts. This meta-analytic study was conducted to evaluate the risk of infection and revision in pediatric patients after autograft and implant cranioplasty.

**Methods:** A systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A thorough literature search was conducted on PubMed, Cochrane, Scopus, and ScienceDirect database. Articles published from 2000 to 2021 were selected systematically using PRISMA based on the predetermined eligibility criteria. The relevant data were, then, analyzed and discussed.

**Results:** A total of four publications investigating the outcome of autograft and implant cranioplasty were included and reviewed. Postoperative infection and revision rate after 126 cranioplasty procedures (both autograft or implant) from 119 patients below 21 years during time frame of study were analyzed. This meta-analysis study showed that the rate of infection and revision after cranioplasty were not different between the autograft and implant groups.

**Conclusion:** Autograft and implant cranioplasty have no significant difference in postoperatively infection and revision rate. This study showed that cranioplasty using implant is a plausible option in pediatric patients with cranial defects, depending on the patients' condition due to similar outcome with autograft cranioplasty. Further studies with larger population and more specific details are necessary to determine the comparison of autograft and implant material in cranioplasty procedure.

**Keywords:** Autograft cranioplasty, Implant cranioplasty, Infection, Revision

## INTRODUCTION

Cranioplasty is widely known as a reconstructive procedure to repair or close a cranial defect. This procedure is generally performed in cases of trauma, tumor, decompressive craniectomy, infection, and congenital abnormalities.<sup>[1]</sup> In pediatric patients, this procedure is not only necessary to give cerebral protection and prevent trephined syndrome but also to prevent impairment of brain development.<sup>[26]</sup>

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Autologous bone graft is previously considered as biocompatible, having low risk of infection, as well as allergenic and tend to elicit immune response, thus making autograft preferable than implant in this matter. This procedure, however, has a high rate of bone flap resorption mostly in pediatric patients (below 8 years).<sup>[1,21]</sup> Furthermore, the availability of autologous bone from donor site in pediatric patients is limited, particularly in case of large cranial defect.

Several studies have shown that bone replacement materials can be used as alternatives in cranioplasty. Commonly used implant materials for cranioplasty include titanium mesh, polymethylmethacrylate (PMMA), polyetheretherketone (PEEK), and polyethylene.<sup>[3,8]</sup> Implant materials can be adjusted and are easier to reshape to fit the defect contour and size.<sup>[11,8,15]</sup> Furthermore, some studies showed that the risk of infection in cranioplasty using implant materials is not different than autograft.<sup>[19,28]</sup>

The choice of cranioplasty material in pediatric is still debatable. Pediatric patients have characteristics of relatively thinner scalp and calvarial bone than adult, growing cranium size, and limited resources of autologous bone for autograft, thus making cranioplasty more challenging and intricate.<sup>[6,15]</sup> Unlike in adult population, the data directly comparing the outcome of autograft and implant cranioplasty in pediatric patients are limited. This meta-analytic study evaluates the risk of infection and revision rate in pediatric patients following autograft and implant cranioplasty. This study is expected to provide information and help clinicians in the decision-making process to choose the ideal material for cranioplasty in pediatric patients.

## MATERIALS AND METHODS

### Literature search strategy

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>[22]</sup> Studies were obtained from a thorough search on PubMed, Cochrane, Scopus, and ScienceDirect database in July–August 2021 using Boolean operator with keywords (“cranioplasty” OR “osteoplasty”) AND (“pediatric” OR “children” OR “child” OR “pediatric”) AND (“implant”) AND (“outcome” OR “complications”).

### Eligibility criteria

We included studies in English or Bahasa language, randomized controlled trial, and prospective or retrospective studies in pediatric patients aged below 21 years who underwent autograft cranioplasty only or implant cranioplasty only. Only studies reporting infection and revision rate in the follow-up period after surgery were included in the study.

Reviews, unpublished articles, letters to editor, abstracts, case report or series, and studies not written in English were excluded from the study.

### Selection of articles

All records on the title and abstract were screened. Duplicates were then eliminated and three authors (DRA, MAP, and BU) independently assessed potentially relevant studies based on the eligibility criteria. The reasons of exclusion were noted and reported. Included studies for further analysis are summarized in Table 1.

### Assessment of study quality and risk of bias

All included studies for further analysis were independently reviewed by the authors to determine the risk of bias using Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) for nonrandomized studies based on Cochrane Handbook for Systematic Reviews of Interventions. Discrepancies between reviewers were resolved by discussion or involvement of third-party assessors.<sup>[12]</sup>

### Data extraction

Data extraction from articles was performed independently by two authors (DRA and MAP). The extracted data were collected by the authors, including, year of publication, study design, patient demographic, follow-up period, type of cranioplasty, rate of infection and revision procedure, and graft's materials. Infection was defined as any occurrence of infection related with the cranioplasty that was reported in selected studies during follow-up period. Revision was defined as any surgical procedure to replace or remove the graft after the cranioplasty procedure.

### Statistical analysis

The total number of cranioplasty procedures as well as infection and rate of revision were distinguished based on the types of material (autograft and allograft/implant). Rates of infection and revision were then calculated (pooled) and compared for all materials. A sub-analysis of outcome in autograft method using full-thickness bone flap was performed. Meta-analysis was then performed with RevMan software version 5.4.  $P < 0.005$  was considered statistically significant.<sup>[22]</sup>

## RESULTS

### Study characteristics

We identified and screened 203 studies including PubMed (118 literature), Cochrane (1 literature), Scopus (49 literature), and ScienceDirect (35 literature). Identification of duplicates

Table 1: Study characteristics.

Author	Year	Design study	Age (month)		Gender (%)		Follow-up (month)		Graft (%)		Infection (%)		Need for revision (%)		Description	
			Mean	Min-Max	M	F	Mean	Min-Max	Autograft	Implant	Total	Autograft	Implant	Auto		Implant
Josan et al.	2005	Retrospective cohort	97.2	1.4-180	-	-	-	-	28 (87.5)	4 (12.5)	32	3 (10.7)	0	5 (17.9)	0	Autograft: - Full-thickness bone flap=20 - Split calvarial=8 Implant: PMMA=3, titanium plate=1
Martin et al.	2014	Retrospective cohort	115.85	1-204	21 (77.8)	7 (25.93)	83	18-154	20 (60.6)	13 (39.4)	33	2 (10)	1 (7.7)	8 (40)	3 (23.1)	Autograft: Bone flap=20 Implant: PMMA=13
Gilardino et al.	2015	Retrospective cohort	127.2	48-192	13 (65%)	7 (35%)	-	-	15 (75)	5 (25)	20	0	0	2 (13.3)	0	Autograft: Split bone grafts=15 Implant: PEEK=5
Fu et al.	2016	Retrospective cohort	88.8	12-228	27 (65.85)	14 (34.14)	27.9	1.2-108	11 (26.83)	30 (73.17)	41	0	0	1 (9)	0	Autograft: - Split calvarial=7 - Bone particulates=4 Implant: - Polyethylene=9 - PMMA=15 - PEEK=2 - Alloplastic unspecified=1 Titanium=3

and screening through titles and abstracts were carried out resulting in a total of 158 literatures obtained. Full-text screening was then carried out, and 119 literatures were then excluded based on the appropriate eligibility criteria [Figure 1]. A total of 39 studies were assessed for feasibility and four studies were included in the qualitative review and meta-analysis. Detailed data of each study are shown in Table 1.

**Study quality assessment**

The risk of bias assessment of the involved studies was analyzed using ROBINS-I for *nonrandomized*. The result of the risk analysis for bias is shown in Figure 2.

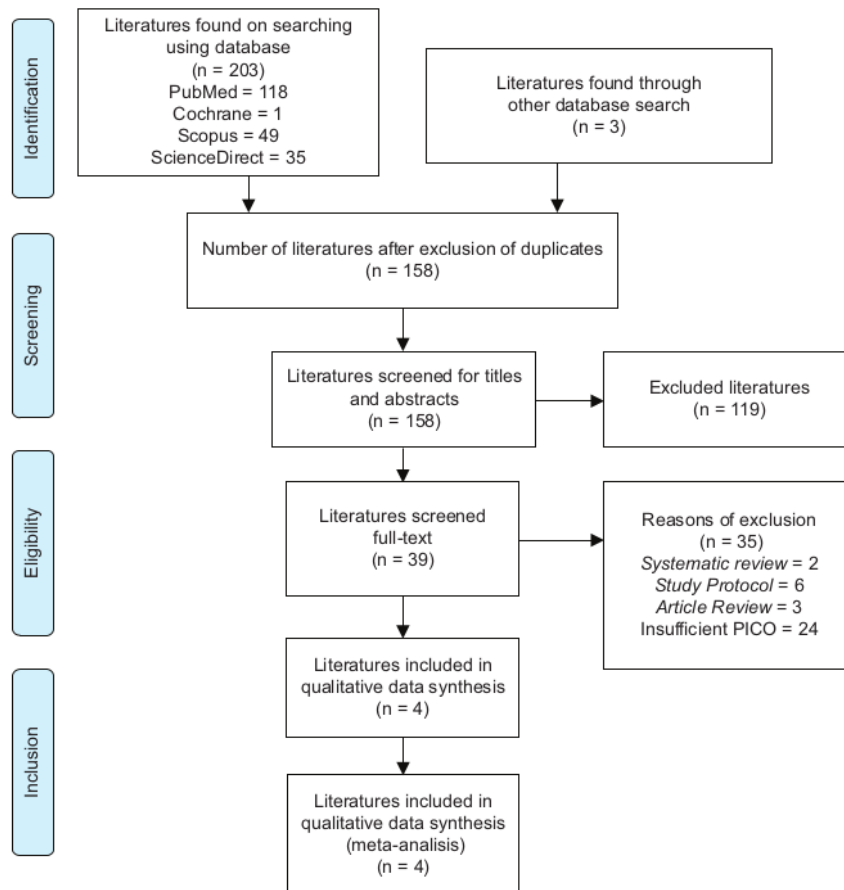
Missing data were found to be the highest risk of bias in the studies included in this systematic review. This is due to incomplete patient outcome data that reported in the study by Josan *et al.* and Fu *et al.*<sup>[8,14]</sup> Outcomes are reported in the form of overall data and not in individual

form so that it can lead to the potential for an analysis that is less accurate or not in accordance with reality, but, in general, it does not affect the conclusions of the study significantly.<sup>[27]</sup>

**Study results and analysis**

Demographics of all studies included in this meta-analysis are presented in Tables 2 and 3.

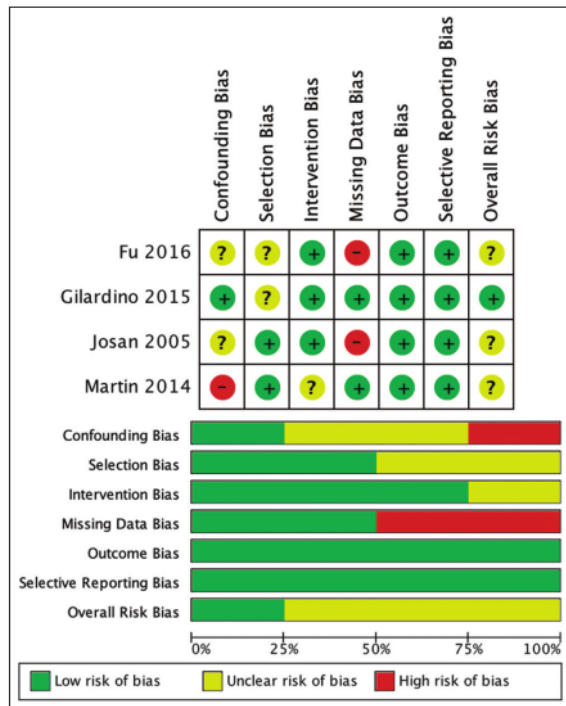
Quantitative analysis showed that patients undergoing *autograft* cranioplasty had a risk of infection that was not much different from patients undergoing implant cranioplasty (RR = 1.26; 95% CI 0.21–7.46; P = 0.80). The heterogeneity analysis showed that the results were very homogeneous, with an I<sup>2</sup> of 0% [Figure 3]. The subgroup analysis showed that the risk of infection was not much different in autograft full-thickness cranioplasty group with implants (RR = 1.45; 95% CI 0.25–8.53; P = 0.68) with very low heterogeneity (I<sup>2</sup> = 0%) [Figure 4].



**Figure 1:** Flowchart of the searched literature.

Analysis of the risk ratio for the need for revision of the autograft and implant groups showed that the patients who received autologous bone as a graft for the cranioplasty had no difference risk of requiring revision compared to patients who had implanted cranioplasty (RR = 2.08; 95% CI 0.83–5.25;  $P = 0.12$ ). The heterogeneity analysis showed

that the results were very homogeneous with an  $I^2$  of 0% [Figures 5 and 6]. The result of subgroup analysis showed that the risk value that needed to fixed revision was not much different in autograft full-thickness cranioplasty group with implants (RR = 1.89; 95% CI 0.66–5.46;  $P = 0.24$ ) with very low heterogeneity ( $I^2 = 0\%$ ) [Figure 7].



**Figure 2:** Risk assessment bias. The risk assessment of bias used ROBINS-I for nonrandomized studies in each study (above) and the proportion of risk assessment results for bias using ROBINS-I for nonrandomized studies (below).

## DISCUSSION

Cranioplasty materials can be broadly divided into two types, namely, autologous bone and other bone/implant replacement materials such as PEEK, titanium, polyethylene, and PMMA.<sup>[2,6,9]</sup> Each material has been known to have its own advantages and disadvantages, such as in the risk of postcranioplasty infection.<sup>[20]</sup>

This review compared the rate of infection between autograft cranioplasty with the implant. The comparison between autograft cranioplasty and implant overall showed that the result was not much different from the infection risk aspect in the two groups where the results of this effect were not statistically significant after being analyzed. Two studies that provide the data related to this are the study by Josan *et al.* and Martin *et al.*<sup>[14,21]</sup> Analysis shows that both studies have similar conclusions between groups, namely, the use of autologous bone has a risk of infection that is not different from the use of implants. Different aspects of the characteristics of each material also play an important role in the risk of infection: material properties, biocompatibility, bioactivity, and others.<sup>[18]</sup> Bone storage method has potential for infection and bone resorption which can render the autologous bone flap unusable later.<sup>[13,16]</sup> This result was contradictive to the study by Rocque *et al.* who reported no significant association between storage method and infection.<sup>[24]</sup>

Other materials, namely, implants, also have different characteristics for each material with their respective

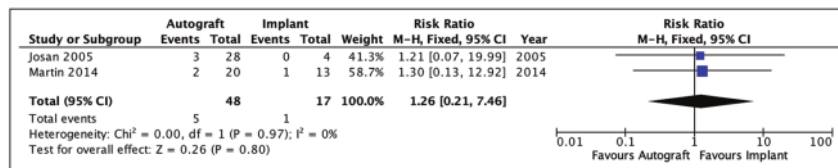
**Table 2:** Demographic characteristics of the studies.

Description		Extractable study n/4 (%)	Total n (%)
Total patients	n	4 studies (100%)	113 patients
Total operations	n	4 studies	126 operations
Average age	Month (avg)	4 studies (100%)	103.74 months
Gender	n	3 studies (75%)	91 patients
Male			62/91 (68.1%)
Female			29/91 (31.9%)
Follow-up	Month (avg)	2 studies (50%)	29.18 months
Cranioplasty material	n		
Autograft		4 studies (100%)	74/126 operations (58.7%)
Implant		4 studies (100%)	52/126 operations (41.3%)
Outcome			
Infection	n	2 (50%)	6/126 operations (4.8%)
Need for revision	n	4 (100%)	19/126 operations (15.1%)

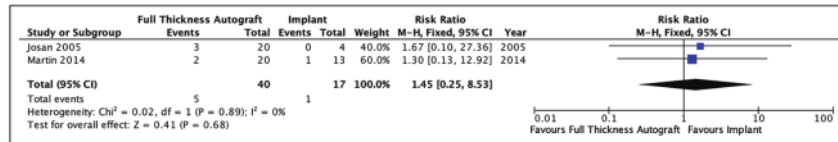
**Table 3:** Graft type used.

Graft type	Extractable study n/4 studies (%)	Total n (%)
Autograft		74/126 operations (58.7%)
Craniectomy flap	2 studies (50%)	40/74 operations (54.1%)
Split calvarial graft	3 studies (75%)	30/74 operations (40.5%)
Bone particulate	1 study (25%)	4/74 operations (5.4%)
Implant		52/126 operations (41.3%)
Polyethylene	1 study (25%)	9/52 operations (17.3%)
PEEK	2 studies (50%)	7/52 operations (13.5%)
PMMA	3 studies (75%)	31/52 operations (59.6%)
Titanium	2 studies (50%)	4/52 operations (7.7%)
Alloplasty (unspecified)	1 study (25%)	1/52 operations (1.9%)

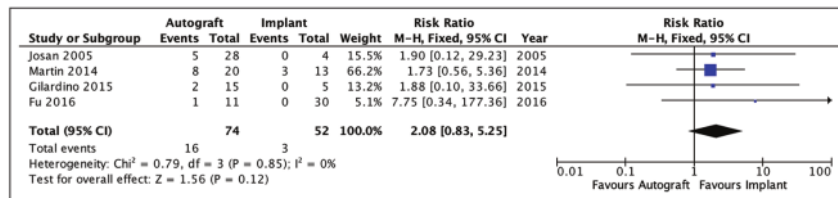
PEEK: Polyetheretherketone, PMMA: Polymethylmethacrylate



**Figure 3:** Analysis of the infection risk ratio of the autograft and implant groups. The risk of infection was not different in the autograft and implant groups. The results of the calculation of heterogeneity showed a very low number (RR = 1.26; 95% CI 0.21–7.46; P = 0.80).



**Figure 4:** Analysis of infection risk ratio in full-thickness autograft and implant groups. The risk of infection was not different in the full-thickness autograft with implant group. Very low heterogeneity results (RR = 1.45; 95% CI 0.25–8.53; P = 0.68; I² = 0%).



**Figure 5:** Analysis of the risk ratio for the need for revision of the autograft and implant groups. The need for revision in the autograft group with implants was not much different. Very low heterogeneity results (RR = 2.08; 95% CI 0.83–5.25; P = 0.12; I² = 0%).

risks.<sup>[4,18]</sup> Analysis of all implant materials as a whole did not show any difference in autologous bone having almost similar infection rates with hand-formed PMMA and hydroxyapatite.<sup>[18]</sup> The lowest risk of infection was found in polyethylene materials from the literature reviewed (5.93%, compared to hand-formed PMMA at 10.98%). PMMA with other preparation measures, such as templated (6.86%)

and prefabricated (6.99%), had lower risk of infection than hand-formed ones. It is also thought that the presence of one of the patients who had a history of infection before autologous material cranioplasty might have influenced the results of this review in the study by Martin *et al.*<sup>[21]</sup> The previous infection can be a confounding factor in the overall risk of infection.

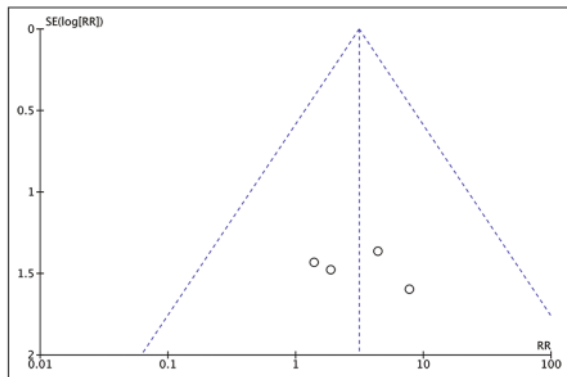
All four studies showed that patients who received autologous bone as a cranioplasty material had no difference in the need of revision than patients who had implanted cranioplasty. Subgroup analysis showed that the risk of needing revision was not significantly different in the full-thickness autograft cranioplasty group with numbers remaining statistically insignificant. Revision cranioplasty is generally performed if there are complications such as infection, osteolysis and resorption of the flap, and lose or broken fixation between the flap and bone so that the flap shifts.

Osteolysis is a major complication of pediatric cranioplasty, 12 of 18 patients (66.7%) developed osteolysis within 6–12 months, and 8 of these patients (44.4%) required follow-up surgery for bone flap replacement with PMMA or CAD cranioplasty. Revised cranioplasty on autograft material can also be caused by nonossification/disintegration of the graft. Osteolysis due to bone flap resorption is a major cause of revision cranioplasty in pediatric patients. Osteolysis is known to resolve spontaneously in some cases, so a “wait and see” procedure may be considered in cases of osteolysis occurring in pediatric patients. The highest rate of bone resorption occurs in the early growth phase to 7 years of age and declines significantly over a period of time between 8 and 14 years. Bowers *et al.* even reported a younger age of  $\leq 2.5$  years age

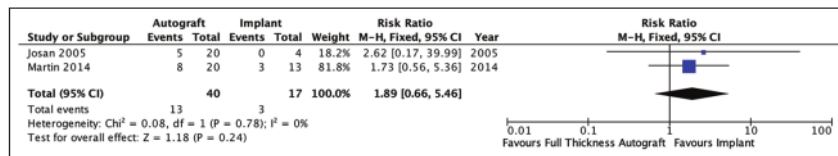
of having high resorption rate. It was hypothesized to be caused by the rapid head growth and high metabolic demand, exceeding bone flap’s capability to fuse with the recipient site,<sup>[5]</sup> while adolescent patients between the ages of 15 and 18 years have already had complete calvarial growth. These changes had made the patient’s age on cranioplasty decision important. This statement was, further, backed by Rocque *et al.* in their study, reporting a 1% decrease of the risk of resorption with each increasing month of age.<sup>[24]</sup>

We often encounter problems in large cranioplasty defects at our institution using autologous bone graft. High resorption rate limits the area that could be reconstructed if the surgeon chooses to solely use preserved bone graft. Additional bone grafts were often needed from other donor site. This procedure could lead to other potential problem. According to Grant *et al.*, bone flaps larger than 75 cm<sup>2</sup> showed up to 60% higher flap resorption rates than smaller (0%) bone flaps.<sup>[10]</sup> Lack of a local dura mater can lead to disruption of the orderly growth of the cranium and is thought to affect bone flap resorption in pediatrics. Placement of autologous bone flaps in more than 6 weeks after the initial surgery is estimated to cause a 3-fold increase in the occurrence of osteolysis.<sup>[23]</sup> It is also stated that osteoinductive capacities were decreased after the age of 2.<sup>[11]</sup> Other factors, including thinner calvarial thickness in younger pediatric patient, might decrease the surface area of cancellous part of the bone in contact between donor and recipient site.<sup>[17]</sup>

Josan *et al.*, in their study, found that 4 out of 24 cases (16.6%) who underwent autograft cranioplasty experienced complications of infection and wound dehiscence that required revision cranioplasty.<sup>[14]</sup> In a study conducted by Martin *et al.*, there was no infection in the bone flap of 18 patients under the age of 15 years, whereas 22.2% and 12.8% of infection cases occurred in adolescents and adults.<sup>[21]</sup> A study by Bowers *et al.* also showed a higher infection rate in younger patients. Other implant materials might be explored further to become the main choice for pediatric cranioplasty, replacing autologous bone graft due to no difference in infection rate. Aside from lower infection rate, report of high success rate of synthetic flap also increased its potential usage as standard pediatric cranioplasty material replacing autologous bone graft.<sup>[5]</sup> Its unabsorbable nature could become



**Figure 6:** Funnel plot for the analysis of need of revision between the autograft and implant cranioplasty. The “O” referring to the included studies for the analysis of need of revision between the autograft and implant cranioplasty subgroup as the forest plot [Figure 5].



**Figure 7:** Analysis of the risk ratio requirement for revision of the full-thickness autograft and implant groups. The risk of needing a revision was not much different in the two groups where this result was not statistically significant. The calculation results show a very low heterogeneity (RR = 1.89; 95% CI 0.66–5.46; P = 0.24; I<sup>2</sup> = 0%).



the solution for resorption problem, especially for children under the age of 8 with PMMA showing the most promising potential compared to other materials.<sup>[21]</sup>

### Limitations

There were only limited publications comparing cranioplasty material in pediatric population. Among eligible studies, only one publication provides complete individual data which could make analytic bias due to unrecognized confounding factors. The amount of data may hinder more accurate information interpretation, although we believe that the methodology provided is properly applied in this analysis.

Different time to surgery among papers could also lead to different occurrences of cases (resorption or infection) from different types of intervention. The lack of standardized nor homogeneity among the studies, and possibly in among the subjects of each studies, may be in risk of conclusion misinterpretation, that is, more subjects who experienced infection underwent shorter duration from first surgery to cranioplasty, while those whom require revision may have risk in only one type of bone such as the resorption risk in autologous bone which is not present in implants.

The causes for revision in each subjects from different studies are also not differentiated and analyzed, meaning that different types of grafts with different tendency of complication may affect the analysis, leading to a nonapplicable conclusion.

Unstandardized autologous bone graft storage method between the selected studies could also be a factor for high infection rate. Moreover, the risk of revision may be different in those who received implants due to the growing skull of pediatric patients, and depending on the period of follow-up of each study, this aspect may confoundly affect the outcome of the analysis.<sup>[7,25]</sup>

### CONCLUSION

The results of a meta-analysis of four literatures discussing the comparison of the outcomes of autograft and implant cranioplasty in the pediatric population show that outcome of infection did not differ in the implant group compared to the autograft group. The rate of need for revision was also not different in the implant group compared to the autograft group. The results of the subgroup analysis comparing the full-thickness autograft cranioplasty group with the implant cranioplasty group also did not differ between the infection outcome and the need for revision.

The author suggests that implant materials can be used as an option in pediatric patients with cranial defects by taking each patient's condition into account. Larger, specific studies are needed to determine the comparison of outcomes between autograft cranioplasty and implant cranioplasty in

the pediatric population. Other factors that can affect long-term outcomes such as the choice of cranioplasty material from the start, storage and preparation of the material, and the condition of the patient at the start of the cranioplasty procedure also need to be included in further analysis.

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### Authors' Contributions

DRA: Conceived and planned the study protocol, search strategy, literature search, systematic review, literature appraisal, data extraction, data synthesis, lead in manuscript writing, and final version of manuscript. MAP: Conceived and planned the study protocol, literature search; systematic review, literature appraisal, data extraction, manuscript writing and editing, and final version of manuscript. BU: Planned the study, conceptualization, search strategy, data extraction, manuscript writing and editing, critical review, and final version of manuscript. AAF: Conceived and planned the study, literature search; systematic review, literature appraisal, data extraction, manuscript writing and editing, final version of manuscript, and submitting for publication. EAS: Conceived and planned the study, literature search; systematic review, literature appraisal, data extraction, manuscript writing and editing, final version of manuscript, and submitting for publication. AS: Conceived and planned the study, literature search; systematic review, literature appraisal, data extraction, manuscript writing and editing, final version of manuscript, and submitting for publication.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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# Comparison of autograft and implant cranioplasty in pediatrics: A meta-analysis

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