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An investigation of factors associated with the development of postoperative bone flap infection following decompressive craniectomy and subsequent cranioplasty

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ABSTRACT

Objective: After a decompressive craniectomy (DC), a cranioplasty (CP) is often performed in order to improve neurosurgical outcome and cerebral blood circulation. But even though the performance of a CP subsequent to a DC has become routine medical practice, patients can in fact develop many complications from the surgery that could prolong hospitalization and lead to unfavorable prognoses. This study investigates one of the most frequent complications, bone flap infection, in order to identify prognostic factors of its development.
Patients and Methods: In this single-center study, we have retrospectively examined 329 CPs performed between 2002 and 2017. Multiple categorical and metric parameters (e.g., timing of CP, bone flap material, specific laboratory signs of infection and reason for DC) were analyzed applying unadjusted and multivariable testing.
Results: Bone flap infection occurred in 24 patients (7.3%). A CP performed more than six months after a DC is associated with a significantly increased risk of infection (OR = 0.308 [0.118; 0.803], p = 0.016). However, with CPs performed after twelve months, the incidence decreases, but without provable statistical impact. In addition, bone flap infection is strongly related to the neurological outcome and the material used for the skull implant, with the use of synthetic bone flaps leading to a marked increase in the rate of infection ($p < 0.001$).
Conclusions: This study supports the hypothesis that the risk of infection is higher the longer the elapsed time between DC and CP, especially if more than six months. Based on our results, the best DC-CP time frame for keeping the infection rate low is performing the CP within the first six months after the DC. In the event that the CP cannot be performed within the first six months, a CP performed twelve months or more after the DC seems to have a favorable outcome as well.

1. Introduction

Decompressive craniectomy (DC) is the preferred treatment for relieving increased intracranial pressure in patients with refractory intracranial hypertension, which can occur in conjunction with various medical conditions (e.g., intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury and ischemic stroke [1,2]. Performed after a DC, a cranioplasty (CP) leads to improved cerebral blood circulation and neurosurgical outcome [1–3], the latter not merely in terms of cosmetic appearance but, more importantly, for the protection of the brain. There are also studies that have reported on its positive influence on the hydrodynamics and metabolism of cerebrospinal fluid (CSF) [3–6]. *Syndrome of the trephined*, a disorder specifically involving motor, cognitive and language deficits, is a condition that is usually alleviated by the performance of a CP as well [7–9].

Either autologous bone flap harvested at the time of a DC or synthetic materials such as polyether ether ketone (PEEK) can be used to perform a CP [7,10,11]. Although CP is a safe surgical procedure, it is, nonetheless, associated with several complications and risks. Not only infection, but also aseptic bone flap resorption, bleeding, pseudomeningocele collection and wound-healing disorders can all come into play [1,12–16]. In contrast to the practices in place for DC, there are no uniform guidelines for CP, particularly regarding the optimal timing for the procedure. In fact, there are several conflicting opinions as well as contradictory evidence regarding its optimal timing. Some authors advise a period of a few months between DC and CP, while others

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advise waiting at least one year before the CP is performed [2,13,16].

The purpose of this single-center study was to investigate one of the most frequent complications that can occur after CP—infection of the bone flap—as it occurs within the framework of the timing of the CP and to exploratively determine factors influencing the development of this complication. Several parameters were investigated in order to identify prognostic factors for the development of infection. Particular consideration was given to specific laboratory signs of infection as well as bone flap size as risk factors for the development of a bone flap infection, which to our knowledge had never been investigated before.

2. Materials and methods

In this study, we have retrospectively examined CPs performed at the Otto-von-Guericke University Magdeburg. Only patients receiving their first CP (unilateral hemicraniectomy; frontotemporoparietal) were included in the study. From January 2002 to December 2017, a total of 329 patients (195 men and 134 women) underwent a CP. The initial DCs for these patients were necessary because of conditions that caused increased intracranial pressure, such as traumatic head injuries, stroke or intracranial hemorrhages. After DC, the bone flaps were packed in sterile bags and stored at - 80 °C under aseptic conditions. For subsequent CP, these bone flaps were removed from the freezer and thawed at room temperature approximately two hours before reimplantation and during surgery fixed in situ with mini plates and/or titanium clamps.

The main purpose of this study was to exploratively investigate the parameters affecting the incidence of infection after a CP. The following parameters were evaluated:

- CP timing (time elapsed between DC and CP [< 3 months, 3–6 months, > 6 months])
- Age of patient [years]
- Size of bone flap [cm^2]
- Number of bone flap parts
- Karnofsky performance score (KPS) [pre- and post-CP]
- Reason for DC
  - Trauma
  - Stroke
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
  - Tumor
  - Infection
  - Other
- Laboratory signs of infection (boolean: is TRUE, when one of the following conditions is fulfilled)
  - C-reactive protein [> 5 mg/l]
  - White blood cells [> 10.4 Gpt/l]
  - Platelet count [> 400 Gpt/l]
- Previous radio- and/or chemotherapy (boolean)
- Localization of DC [left or right hemisphere]
- Diabetes mellitus (boolean)
- Bone flap material
  - Autologous
  - Polyether ether ketone (PEEK)
  - Polymethyl methacrylate (PMMA)
- Ventriculoperitoneal shunting [before, simultaneous to, or after CP]
- Length of surgery and intraoperative blood loss

In our clinical routine, after DC bone flaps were freed from adherent soft tissue residuals, they were separately packed in sterile bags and kept at -80 °C under aseptic conditions. In preparation for a CP, bone flaps were removed from the freezer and thawed at room temperature. Preoperative single-shot antibiotics were always administered with cefalosporin, cefazolin or, in patients with intolerance to both of those antibiotics, clindamycin. During surgery, the scalp flap and temporalis muscle were dissected and separated from the underlying dura or dura substitute, the bone flaps were reimplanted after removal of fibrous tissue from the bony edge of the skull defect and dural tack-up sutures were inserted through the bone flap. Subsequently, skull implants were fixed to the skull using mini plates and/or titanium clamps. Finally, a subgaleal Jackson-Pratt drain was put in place. After the CP, the patients were usually treated in the general ward after a monitoring phase overseen by anaesthetists.

The timing of the CP is defined as the amount of time that elapses between the DC and the bone flap replacement procedure. We compared patient groups with CP occurring less than three months after DC to those whose surgeries were performed between three and six months after DC and to those whose surgeries were conducted more than six months after DC. Since we believed that the impact of an initial trauma could also be a cause of elevated infection rates, a separate analysis was conducted to investigate that possibility.

A bone flap was considered infected if at least one of the following clinical signs was present:

- Wound dehiscence with resulting exposure of the bone flap
- Purulent fluids
- Fluid drainage with signs of infection and fever
- Abscess and empyema

The first postoperative cranial computed tomography (CT) scan was conducted during hospital stay and served as a reference for follow-up, which was routinely three months after CP and, after that, annually. The mean follow-up time was 13.2 ± 25.0 months (median: 3 months, range: [0.3–161.8] months). The patients' conditions were assessed at each follow-up using the KPS. The individual postoperative KPS was determined at last follow-up.

Bone flap infection was treated by skull implant removal, abscess drainage and subsequent treatment with antibiotics according to standard treatment recommendations [17–21]. Antibiotic agents were adapted depending on the causative pathogen and its resistance pattern.

2.1. Statistical analysis

Statistical analyses were performed using the software SAS 9.4 (SAS Institute, Inc., Cary, NY, USA), and since this was an exploratory analysis, deliberately reviewed to the full level of significance. Each p-value ≤ 0.05 thus represents a statistically significant result. For unadjusted analyses, chi-square tests were used for categorical variables and the robust *t*-test (Satterthwaite) for continuous variables.

To assess influence factors in multivariable analyses, the binary logistic regression model was used; this first model included CP timing, specific laboratory signs of infection and bone flap size, all of which had been assumed to have an influence on the rate of infection (a priori hypothesis). A second multivariable model included the factors that were found to be significant in the univariate analysis. Estimates for pairwise odds ratios (OR) and the corresponding 95% confidence interval based on the Wald test were presented.

3. Results

In the cohort we studied, a total of 329 CPs were performed from 18-2,199 days (mean 182.3 ± 194.1 days) after the initial DC. Patients' ages were between two and 91 years (with a mean of 51.2 ± 17.0 years). The most frequent indications for DC were traumatic brain injury (36.2%), ischemic stroke (29.2%), subarachnoid hemorrhage (11.6%), intracerebral hemorrhage (12.8%) and intracranial tumors (6.4%). Table 1 shows both the sex distribution and the initial reason for the DC in relation to the timing of the CP. Additionally, Table 2 shows patient age, KPS and size of the bone flap in relation to CP timing.

Table 1
Sex and reason for decompressive craniectomy by cranioplasty timing (*leukoencephalopathy and non-traumatic subdural hematoma).

		Cranioplasty timing					
		< 3 months		3-6 months		> 6 months	
		N	%	N	%	N	%
Sex	Male	50	71.4	91	57.6	54	53.5
	Female	20	28.6	67	42.4	47	46.5
Reason for decompressive craniectomy							
	Trauma	33	47.1	53	33.5	33	32.7
	Stroke	19	27.1	49	31.0	28	27.7
	Intracerebral hemorrhage	9	12.9	19	12.0	14	13.9
	Subarachnoid hemorrhage	5	7.1	24	15.2	9	8.9
	Tumor	3	4.3	5	3.2	13	12.9
	Infection	1	1.4	3	1.9	3	3.0
	Other*	0	0.0	5	3.2	1	1.0

Bone flap infection occurred in 24 patients (7.3%). Fig. 1 shows the impact of the CP timing on the infection rate. CPs performed between six and twelve months after DC were associated with infection rates of more than 40%. Results of unadjusted analyses of relevant categorical parameters that might influence bone flap infection are shown in Table 3 (categorical variables). The infection rate was significantly influenced by CP timing ($p = 0.010$). 70 patients underwent CP within three months of the DC; infection developed in 3 of those patients (4%, 3 autologous skull implants). The number of patients who underwent a CP within three to six months after the DC was 158; 7 of those patients (4.4%, 4 autologous and 3 synthetic skull implants) developed an infection. In 101 patients who underwent surgery six months or more after the DC, the infection rate was 13.8% (14 patients, 11 autologous and 3 synthetic skull implants). In 10 out 24 patients (42%) cultures yielded infections with *Staphylococcus aureus*. In 5 patients (21%) infections with coagulase-negative staphylococci were proofed. In 5 other patients (21%) culture results remained sterile. The remaining results comprised mixed infections, mainly with viridans streptococci.

The significant influence of CP timing was confirmed by multivariable analysis ($p = 0.025$), which included specific laboratory signs of infection and bone flap size as additional covariables. Classifying into the three categories (< 3 months, 3–6 months, > 6 months) separates out the data in a way that shows that higher infection rates are significantly more probable at time intervals greater than six months (< 3 months vs. > 6 months: OR = 0.292 [0.080; 1.072], $p = 0.064$; 3–6 months vs. > 6 months: OR = 0.308 [0.118; 0.803], $p = 0.016$). A CP performed more than six months after a DC is associated with a significantly increased infection rate.

The unadjusted statistical analysis also revealed that bone flap infection is strongly related to the material used for bone flap replacement, with the use of synthetic bone flaps leading to a significantly increased risk of infection ($p < 0.001$). An autologous bone flap was used in 303 cases (92.1%), while synthetic skull implants were used in 26 cases. While 18 of 303 patients who were given an autologous bone flap developed an infection, this only corresponds to an infection rate of approximately 6%. Yet 6 out of the 26 patients who were given a bone flap made of synthetic material developed an infection, which corresponds to a distinct infection rate of 30% ($p = 0.001$).

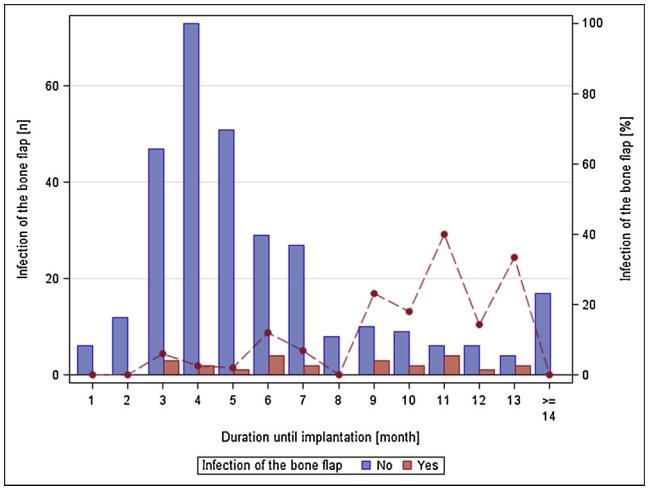

Fig. 1. The LOESS graphic shows the impact of CP timing on infection rate. CPs performed between six and twelve months after decompressive craniectomy are associated with infection rates of more than 40% (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

The analyses of all other categorical parameters (reason for DC, localization, diabetes, specific laboratory signs of infection, previous radio- and/or chemotherapy, ventriculoperitoneal shunting) revealed no significant impact on the frequency of occurrence of bone flap infection.

Table 4 (continuous variables) demonstrates that there was no significant difference between bone flap size, patient age, number of bone flap parts or perioperative parameters (length of surgery and intraoperative blood loss) in terms of infection. Patients who had had a higher KPS before and after CP had a significantly higher infection rate.

Table 2
Patient's age, KPS and bone flap size of decompressive craniectomy by cranioplasty timing.

		Cranioplasty timing		
		< 3 months	3-6 months	> 6 months
Age [years]	N/Mean ± STD	70 / 49.8 ± 18.2	158 / 50.6 ± 17.4	101 / 53.2 ± 15.5
Karnofsky performance score	N/Mean/Median	70 / 0.6 / 0.5	158 / 0.6 / 0.6	101 / 0.6 / 0.6
(preoperative)	[Range]	[0.3-1.0]	[0.3-1.0]	[0.3-1.0]
Size of the bone flap [cm²]	N/Mean/Median	70 / 84.1 / 87.3	158 / 82.6 / 81.7	101 / 75.1 / 77.3
	[Range]	[22.8-123.6]	[23.2-205.7]	[18.5-155.1]

Table 3
Descriptive statistics and results of unadjusted tests for bone flap infection for categorical variables.

		Bone flap Infection				
		Yes		No		
		N	%	N	%	p-value
Trauma	Yes	7	29,2	112	36,7	0.458
	No	17	70,8	193	63,3	
Laboratory signs of infection	Yes	8	33,3	61	20,0	0.122
	No	16	66,7	244	80,0	
Cranioplasty timing	< 3 months	3	12,5	67	22,0	0.010
	3 - 6 months	7	29,2	151	49,5	
	> 6 months	14	58,3	87	28,5	
Radio- and/or chemotherapy	Yes	2	8,3	12	3,9	0.304
	No	22	91,7	293	96,1	
Decompressive craniectomy side	Left	11	45,8	151	49,5	0.729
	Right	13	54,2	154	50,5	
Diabetes	Yes	2	8,3	36	11,8	0.609
	No	22	91,7	269	88,2	
Bone flap material	Autologous	18	75	285	93,4	< 0.001
	Polyether ether ketone	3	12,5	15	4,9	
	Polymethyl methacrylate	3	12,5	5	1,6	
Ventriculoperitoneal shunting	No	22	91,7	273	89,5	0.756
	After the cranioplasty	0	0,0	8	2,6	
	Simultaneously performed	2	8,3	19	6,2	
	Before the cranioplasty	0	0,0	5	1,6	

Table 5 shows that the influence on infection rate of specific laboratory signs of infection and/or the size of the bone flap could not be verified as a priori hypothesized.

Complications, including epidural haematoma, subdural haematoma and intracerebral hemorrhage requiring evacuation, occurred in 7 patients (2.1%). Non-infectious, non-haemorrhagic, extra-axial fluid collection (e.g. pseudomeningocele) occurred in 28 patients (8.5%). Fourteen patients (4.2%) developed seizures postoperatively. Postoperative hydrocephalus necessitating shunt implantation occurred in 29 patients (8.8%).

4. Discussion

Although CP has become routine surgery, patients who have undergone a CP can develop many subsequent complications that could prolong hospitalization and lead to unfavorable prognoses [1,2,14]. Rather than focusing on complications such as postoperative hydrocephalus, non-infectious, non-hemorrhagic, extra-axial fluid collection and seizure activity, we have instead focused our work in this study on the more common complication of infections that can occur within the framework of a CP performed after a DC.

4.1. Cranioplasty timing

There are several conflicting studies on the optimal timing of CP, some advising a time space of a few months between DC and CP and others recommending a wait of at least one year after the DC in order to allow enough time for patient recovery from the underlying disease and reduction of brain swelling [13,16,22–24]. Some authors recommend waiting as long as possible after a DC before performing the CP [25,26], or at the other end of the spectrum, suggest postponing the surgery for only three to six months after the DC [16]. Authors of two other studies express concern about late CP in patients with major cranial defects [15,27]. The infection rate reported in the literature ranges from 1.4% to 24.4% [1,18,28,29]. In the present study, the infection rate of 7.3% appears to be similar to rates reported previously. As mentioned earlier, the timing of bone flap reimplantation is a continuing subject of disagreement in the literature since no study has as yet definitively established a direct relation between CP timing and subsequent complications [29–32].

Our study, in which early CP was clearly associated with a significantly lower infection rate, reflected the findings of several other studies [7]. Analysis of CP timing in the three groups (< 3 months, 3–6 months, > 6 months) indicates that the probability of infection increases with the amount of elapsed time between DC and CP. In the cases studied, the more time that had passed before the CP, the higher the number of infections. Fig. 1 illustrates the CP infection rate, which increases significantly the longer the lapse of time (especially with a lapse of more than six months). Our results are in line with the reviews of Yadla et al. [16], while the work of Gooch and colleagues shows a markedly opposite tendency [28]. Some studies have even found no significant connection at all between infection rate and the timing of

Table 4
Descriptive statistics and results of unadjusted tests for bone flap infection in relation to continuous variables.

		Bone flap infection		
		Yes	No	p-value
Age in years	N / Mean ± STD	24 / 50.0 ± 16.6	305 / 51.3 ± 17.1	0.699
Size of bone flap [cm^2]	N / Mean ± STD	24 / 75.6 ± 36.7	305 / 81.0 ± 23.6	0.486
Number of bone flap parts	N / Mean ± STD	24 / 1.2 ± 0.6	305 / 1.1 ± 0.5	0.887
Karnofsky performance score (preoperative)	N / Mean ± STD	24 / 73.7 ± 21.0	305 / 60.4 ± 20.7	0.007
Karnofsky performance score (postoperative)	N / Mean ± STD	24 / 74.2 ± 21.2	305 / 60.8 ± 21.1	0.006
Glasgow outcome scale (follow-up)	N / Mean ± STD	24 / 3.7 ± 0.9	305 / 3.1 ± 0.9	0.004
Length of surgery (min)	N / Mean ± STD	24 / 110.5 ± 45.2	305 / 97.5 ± 41.8	0.147
Blood loss (ml)	N / Mean ± STD	24 / 146.9 ± 127.3	305 / 144.1 ± 147.3	0.946

Table 5
Results of both multivariable models (a priori hypothesis and significant factors in univariate testing). In contrast to the CP timing and KPS the multivariable analysis shows no impact of laboratory signs of infection, the size and the material of the bone flap on the postoperative infection rate.

					95%-CI	
	p-value		p-value pairwise	OR-estimates	LCL	UCL
Cranioplasty timing	0.025	< 3 months vs. 3-6 months	0.941	0.949	0.237	3.796
		< 3 months vs. > 6 months	0.064	0.292	0.080	1.072
		3-6 months vs. > 6 months	0.016	0.308	0.118	0.803
Laboratory signs of infection	0.203	Yes vs. No	0.203	0.551	0.220	1.379
Size of bone flap	0.666			0.996	0.979	1.013
Karnofsky performance score (preoperative)	0.018			1.297	1.046	1.607
Cranioplasty timing	0.064	< 3 months vs. 3-6 months	0.895	1.098	0.271	4.446
		< 3 months vs. > 6 months	0.130	0.352	0.091	1.360
		3-6 months vs. > 6 months	0.029	0.320	0.116	0.888
Bone flap material (autologous)	0.380	Yes vs. No	0.380	0.587	0.178	1.929

the CP [1,2].

It should be noted that patients who had a CP performed one year or more after the DC showed a less pronounced infection rate; however, due to the relatively small number of patient cases reviewed in the present study, no significant results for that time lapse could be observed. We found no factors that might have explained a prolonged delay before a CP was performed. Any delay was most probably caused by inadequate ambulatory care or by a delay in or a prolonged rehabilitation. In the past, it has commonly been recommended that a CP be performed at least three months after a DC. It has been argued that this period of time is sufficient for postoperative edema to resolve and possibly reduces the rate of infection and hydrocephalus [33]. However, the results presented here are somewhat unique in that we study CPs performed more than six months after a DC, since a CP delayed beyond six months is in fact uncommon.

4.2. Karnofsky performance score

In addition to the results specifically involving the timing of the CP, the present study indicates that there is a significant impact on infection rate from higher KPS as well as from the use of synthetic bone flap material. The higher the KPS, the more likely it is that patients will develop a bone flap infection according to the cases reviewed in our study. It is difficult to explain why patients with a KPS of 70 or higher should be more likely to develop bone flap infections than patients with a KPS of 60 or lower. The main difference between these groups is the fact that patients with a KPS of 70 or higher are considered able to be self-reliant. In contrast, patients with a KPS of 60 or lower usually need professional help from caregivers. It might be possible that this professional help is somehow a protection against the development of wound infections because caregivers perform frequent wound checks and the like.

Our results contrast with the results of Rosseto et al. [21], which found that patients with a poor neurological status have an increased risk of infection because they are somewhat or completely bedridden and possibly malnourished. A possible explanation for these results could be that the patients with a low KPS in the Rosseto study already had a colonization of multi-resistant bacteria on site, thus increasing their susceptibility to common infections such as urinary tract infections or pneumonia [7].

4.3. Skull implant material

CPs performed using synthetic material did show a higher rate of infection than CPs performed using autologous bone flap material, but this result was not confirmed in the multivariable test. One possible reason for that discrepancy may be the overall low number of CPs performed using autologous material in the cases studied here, which leads to relatively low statistical power. However, several other studies have also shown that using synthetic material is indeed associated with a higher risk of infection. Autologous bone material has several advantages, including its perfect shape, weak rejection response, low cost and high patient acceptance rate [18,32,34,35].

More recent synthetic skull implant materials that are constructed with three-dimensional, computer-aided design (CAD) methods are widely used and have led to excellent cosmetic results, although these synthetic materials are still expensive and have a higher suspected risk of infection and rejection [18,32,34–36]. Reimplantation of autologous bone flap is usually the preferred practice as the risk of immune rejection is theoretically lower and its effectiveness as a substrate for bone growth and revascularization appears to be higher [2,37–40]. But again, There are studies that indicate that there is no significant difference in infection rate between autologous and non-autologous material [16].

Some authors have demonstrated that complications occurring after a CP might be influenced by a combination of many factors, including age, reason for the DC, bone lap concavity, sex, comorbidities, material of the skull implant, bone flap localization and time elapsed between DC and CP [7,41,42]. But in the present study, suffering from conditions such as diabetes, having had malignancies in the past, exhibiting signs of infection within laboratory parameters and the initial reason for the DC all played no apparent role in increasing the rate of infection. Furthermore, neither the size of the bone flap nor the sex or age of the patient seemed to have contributed to the development of bone flap infection in this study.

Postoperative hydrocephalus requiring ventriculoperitoneal (VP) shunting was observed in 8.8% of the cases in this study. The hydrocephalus rate in various other studies was reported to be between 1.4% and 12.2% [1,8,29]. Hydrocephalus occurs as a complication in patients after a DC, and several researchers have found a relationship between the timing of the CP and hydrocephalus [43,44]. Some researchers consider combining the CP with a programmable ventriculoperitoneal shunt implant surgery to be useful [43,45], while others report that performing a CP simultaneous to the placement of a VP shunt system has resulted in higher infection rates, especially in patients with severe brain bulging [46,47]. Implantation of a VP shunt system performed at the same time as the CP did not increase the risk of infection in any of the cases in the current study. In addition, a higher infection rate did not appear in cases where a VP shunt system was in place prior to the CP surgery. The rate of other complications, such as epidural hematoma, subdural hematoma, intracerebral hemorrhage requiring evacuation, hygroma and seizure activity, was almost the same as rates in the data from the literature [1,2,8,19,20,29].

4.4. Limitation

The sample size of the single-center study and the retrospective design are crucial limiting factors. It is difficult to evaluate why, for

some patients, the CP was performed more than six months after the DC while most of the remaining patients were operated on within six months. We can only speculate about the reasons for the delay. Therefore, the applicability of the presented results to generalized patient populations is limited.

5. Conclusion

This study supports the assumption that the risk of infection is higher the longer the gap in time between DC and CP, especially if more than six months elapse. Based on our research results, the best time frame for keeping the infection rate low is performing CP prior to six months after the DC. A CP performed twelve months or more after the DC seems to be favorable as well if performance of the CP is not feasible within the first six months.

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