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ORIGINAL COMMUNICATION

Antiplatelet therapy, but not intravenous thrombolytic therapy, is associated with postoperative bleeding complications after decompressive craniectomy for stroke

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Abstract Intravenous thrombolysis (IVT) is an established treatment in patients suffering from acute ischemic stroke (AIS). IVT might increase the risk of postoperative complications if applied prior to decompressive craniectomy (DC). Therefore, we analyzed the management of patients with and without IVT prior to DC. Between 1999 and 2011, DC was performed in 115 patients after AIS. Patients with and without IVT prior to DC were compared regarding perioperative management, postoperative complications and outcome. Postoperative complications were stratified into non-bleeding and bleeding complications. Outcome was assessed using the modified Rankin scale after three months. Two multivariate analyses were performed to identify predictors for postoperative complications and predictors for unfavourable outcome (mRS 4–6). Fifty-two of 115 patients underwent IVT prior to DC (45 %). Forty-four patients were on antiplatelet therapy prior to DC (38 %). Frequency of bleeding complications did not differ significantly in patients with IVT prior to DC compared to patients without. However, bleeding complications occurred significantly more often in patients with antiplatelet use prior to DC ($p = 0.0003$, OR 4.5). In the multivariate analysis "preoperative use of acetylsalicylic acid" was the only independent predictor associated with bleeding complications ($p = 0.002$, OR 3.9). IVT prior to DC did not predict unfavourable outcome. There was no evidence in this observational study that IVT prior to DC places patients at undue risk of bleeding complications after subsequent DC. Patients with or without IVT prior to DC suffered significantly more often from postoperative bleeding complications if antiplatelet therapy was applied before onset of AIS.

Keywords Decompressive craniectomy · Stroke · Tissue plasminogen activator · Thrombolysis

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Introduction

Decompressive craniectomy (DC) is a life-saving procedure in patients with intractably elevated intracranial pressure (ICP) due to cerebral infarction, and has been reported to be safe and to improve clinical outcome [1–3]. Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) is the only approved treatment for selected patients with acute ischemic stroke (AIS) [4–7]. Bleeding complications, especially intracranial hemorrhage (ICH), are a known side effect in patients treated with rtPA for AIS [5, 6, 8]. The profound alterations of coagulation cascades induced by IVT raised concerns that any sort of surgery—especially with a large wound surface as in DC procedures—might lead to intra- or postoperative bleeding and counteract the beneficial effects of both treatments [9]. Higher risk for postoperative bleeding complications has been postulated for patients with intra-arterial thrombolysis previously [10]. However, appropriate management of thrombolysis-associated postoperative bleeding complications is still controversially discussed [11, 12]. We, therefore, analyzed our

prospectively conducted database of patients undergoing DC due to cerebral infarction, with special attention to perioperative management of patients after rtPA treatment and associated postoperative complications.

Methods

From October 1999 to December 2011, DC was performed in 115 patients with intractably elevated ICP due to cerebral infarction of the anterior circulation in our institution. Information including patient characteristics on admission and during the course of treatment, radiological features, administration of IVT, antiplatelet therapy with acetylsalicylic acid (ASA) before hospitalization, vascular risk factors, stroke etiology, infarct location, signs of herniation (unilaterally or bilaterally dilated pupils), laboratory data before and after DC (international normalized ratio, partial thromboplastin time, fibrinogen, platelet counts, hemoglobin), mean duration of DC procedure, and complications after DC were entered into a database. The institutional Ethics Review Board approved the study. Etiology of stroke was assessed according to the TOAST subtype classification system [13].

Thrombolytic therapy

Thrombolytic therapy was administered according to international guidelines [14]. In selected cases (i.e., MRI evidence of substantial perfusion/diffusion mismatch) thrombolysis was performed up to 6 h after symptom onset, being beyond the approved 4.5 h time window. The tPA with a dosage of 0.9 mg/kg (maximum dosage 90 mg) was used with 10 % given as an intravenous bolus, followed by continuous infusion of the remainder over 1 h.

Decompressive craniectomy

The DC procedure was performed in a strictly standardized fashion as previously published in detail elsewhere [15]. In short, a large bone flap of at least 11 × 16 cm was removed, the dura mater was opened in a stellate fashion and no watertight duraplasty was applied. The bone flap was stored under sterile conditions at −80 °C. Cranioplasty (CP) was considered after resolution of brain edema in survivors after approximately three months [16].

In order to prevent possible postoperative bleeding complications after DC, application of hemostatic therapy [substitution of platelets and fresh frozen plasma (FFP)] as well as red blood cell (RBC) transfusion for anemia was determined by the consultant neurosurgeon based on the pre- or intraoperative situation.

Statistical analysis plan

For further analysis, patients with DC due to cerebral infarction were divided into two groups: (1) patients without IVT prior to DC, and (2) patients with IVT prior to DC. Complications of DC were assessed and analyzed. Postoperative complications were stratified into non-bleeding complications (wound healing disturbances or abscesses) and bleeding complications. Postoperative bleeding complications were further stratified into serious and non-serious bleeding complications, depending on if surgical treatment was necessary (serious) or not (non-serious).

Outcome was assessed according to the modified Rankin scale (mRS) after three months. According to previous classifications [9], neurological outcome was stratified into favourable (mRS 0–3) versus (vs.) unfavourable (mRS 4–6).

Statistics

Data analyses were performed using the computer software package SPSS (version 19, SPSS, Chicago, IL). An unpaired t test was used for parametric statistics. Categorical variables were analyzed in contingency tables using Fisher's exact or Chi-square test. Results with $p < 0.05$ were considered statistically significant. In a second step, multivariate analyses were performed using a binary logistic regression analysis to find confounding factors between potentially independent predictors for either the development of postoperative bleeding complications and in a separate analysis for unfavourable outcome. Variables with significant p values in univariate analyses were considered as potentially independent variables in the multivariate analysis. A backward stepwise method was used to construct multivariate logistic regression models with the inclusion criterion of a p value of <0.05. Furthermore, we included variables that had been considered to be relevant or significant throughout the literature (age [17], gender [18], vascular risk factors [19–21], etiology of stroke [17], infarct location [17, 22]).

Results

Patient characteristics

DC was performed in 115 patients with intractably elevated ICP due to cerebral infarction. Overall, 32 of 115 patients (28 %) with AIS suffered from additional preoperative ICH in terms of secondary hemorrhagic transformation (HT). Mean age was 54 ± 12 years. Mean time from onset of

symptoms to DC was 42 ± 35 h. Mean duration of the DC procedure was 74 ± 23 min.

Patient characteristics, including age, sex, as well as data on the DC procedure, outcome and postoperative complications in patients without and with IVT prior to DC are shown in Table 1.

Etiology of stroke, vascular risk factors and infarction area did not differ significantly between patients without and with IVT prior to DC.

Thrombolytic therapy and preoperative laboratory data

Fifty-two of 115 patients (45 %) underwent IVT prior to DC. Mean time from onset of symptoms to DC was 45 ± 40 h. Eighteen of 52 patients (35 %) with IVT prior to DC suffered from preoperative ICH. Therefore, 14 of 63 patients (22 %) without IVT prior to DC suffered from preoperative ICH in terms of secondary HT. A total of 44 patients (38 %) were on ASA for antiplatelet therapy prior to hospitalization and DC. In detail, 21 of 52 patients (40 %) with IVT prior to DC were on ASA treatment compared to 23 of 63 patients (37 %) without IVT prior to DC ($p = 0.7$; Table 1). Laboratory data obtained prior to or after DC including international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen, platelet counts, and hemoglobin did not differ significantly between both groups. Detailed laboratory values prior to and after DC are given in Tables 2 and 3.

Influence of thrombolytic treatment on postoperative complications

Overall, postoperative complications were observed in 23 patients without IVT prior to DC, and in 30 patients with IVT prior to DC (37 vs. 58 %; $p = 0.03$, OR 2.4, 95 % CI 1.1–5).

Postoperative complications included 12 patients suffering from non-bleeding complications (10 %), e.g., postoperative wound healing disturbances or infections, and 41 patients suffering from bleeding complications (36 %).

Non-serious bleeding complications occurred in 16 patients without IVT, and in 21 patients with IVT (25 vs. 40 %; $p = 0.1$). Serious bleeding complications occurred in one patient without IVT, and in three patients with IVT (2 vs. 6 %; $p = 0.3$).

Perioperative hemostatic therapy

Perioperative hemostatic therapy (platelet or FFP substitution) as well as transfusion therapy for anemia was applied in 29 patients without IVT prior to DC, and in 28 patients with IVT prior to DC (46 vs. 54 %; $p = 0.5$). Details are given in Tables 2 and 3. Quantity of hemostatic therapy did not differ significantly between patients with or without IVT prior to DC.

Table 1 Patient characteristics

	DC without prior thrombolysis ($n = 63$)		DC after thrombolysis ($n = 52$)	
	Without ASA medication ($n = 40$)	With ASA medication ($n = 23$)	Without ASA medication ($n = 31$)	With ASA medication ($n = 21$)
Mean age (in years)	56 ± 10	59 ± 10	49 ± 13	53 ± 14
Female sex, *n* (%)	18 (45)	8 (35)	9 (29)	8 (38)
Mean time from onset to DC (h)	34 ± 33	40 ± 28	34 ± 26	54 ± 52
Mean duration of DC procedure (min)	70 ± 20	74 ± 25	79 ± 23	72 ± 24
Signs of cerebral herniation (%)	22 (55)	7 (30)	5 (16)	10 (48)
Favourable outcome (3 mo, mRS 0–3)	10 (25)	2 (9)	9 (29)	1 (5)
Unfavourable outcome (3 mo, mRS 4–6)	30 (75)	21 (91)	22 (71)	20 (95)
Mortality, *n* (%)	7 (18)	3 (13)	2 (6)	2 (10)
Overall postoperative complications	23 (37)[†]		30 (58)[†]	
Non-serious bleeding complications[‡]	5 (13)	11 (48)	9 (29)	12 (57)
Serious bleeding complications[‡]	–	1 (4)	2 (6)	1 (5)
Other complications (e.g. wound healing disturbances, abscesses)	5 (13)	1 (4)	4 (13)	2 (10)

Results did not differ significantly between both groups unless otherwise indicated

Values represent number of procedures unless otherwise indicated (%). Means are given with SDs

ASA acetylsalicylic acid, *DC* decompressive craniectomy, *yrs* years, *hrs* hours, *min* minutes, *mo* months, *mRS* modified Rankin scale

[†] $p = 0.03$, OR 2.4, 95 % CI 1.1–5

[‡] $p = 0.0003$, OR 4.5, 95 % CI 2.0–10.2

Table 2 Perioperative hemostatic therapy in patients without and with thrombolysis treatment prior to DC

	DC without prior thrombolysis ($n = 63$)	DC after thrombolysis ($n = 52$)
RBC transfusion	18 (29)	17 (33)
Platelet infusion	7 (11)	8 (15)
FFP	4 (6)	3 (6)
Preoperative ASA medication	23 (37)	21 (40)
Preoperative laboratory values		
INR	1.16 ± 0.16	1.16 ± 0.14
PTT (s)	36 ± 6	35 ± 6
Platelet count (/nl)	210 ± 67	214 ± 53
Fibrinogen (mg/dl)	406 ± 109	353 ± 176
Hemoglobin (g/dl)	12.2 ± 2.2	12.5 ± 1.6
Postoperative laboratory values		
INR	1.31 ± 0.19	1.28 ± 0.16
PTT (sec)	40 ± 13	37 ± 6
Platelet count (/nl)	184 ± 63	186 ± 41
Fibrinogen (mg/dl)	332 ± 127	296 ± 122
Hemoglobin (g/dl)	9.7 ± 1.7	9.7 ± 1.8
Postoperative complications	23 (37)[†]	30 (58)[†]
Favourable outcome (3 mo, mRS 0–3)	12 (19)	10 (19)

Values represent number of patients unless otherwise indicated (%). Means are given with SDs

DC decompressive craniectomy, *RBC* red blood cells, *FFP* fresh frozen plasma, *ASA* acetylsalicylic acid, *INR* international normalized ratio, *PTT* partial thromboplastin time, *s* seconds

[†] $p = 0.03$, OR 2.4, 95 % CI 1.1–5

Influence of preoperative antiplatelet therapy with ASA

Overall, patients with postoperative bleeding complications received significantly more often ASA prior to DC compared to patients without ASA treatment (57 vs. 23 %; $p = 0.0003$, OR 4.5, 95 % CI 2.0–10.2; Table 1). However, preoperative laboratory values did not differ significantly between patients without and with ASA therapy prior to DC (Table 3). Patients with preoperative antiplatelet therapy with ASA received significantly more often perioperative hemostatic therapy consisting of platelet transfusion (4 vs. 27 %; $p = 0.0009$, OR 8.5, 95 % CI 2.2–32.2) and FFP substitution (1 vs. 14 %; $p = 0.01$, OR 11.1, 95 % CI 1.3–95.3) compared to patients without preoperative ASA therapy. However, postoperative laboratory values including hemoglobin, fibrinogen and platelet count were significantly decreased compared to preoperative laboratory values in patients with preoperative ASA therapy (Table 3).

Table 3 Patients without and with previous ASA medication

	Without ASA medication prior to DC ($n = 71$)	With ASA medication prior to DC ($n = 44$)
RBC transfusion	17 (24)	18 (41)
Platelet infusion	3 (4)[†]	12 (27)[†]
FFP	1 (1)[‡]	6 (14)[‡]
Preoperative thrombolysis	31 (44)	21 (48)
Preoperative laboratory values		
INR	1.16 ± 0.16	1.17 ± 0.13
PTT (s)	35 ± 7	35 ± 5
Platelet count (/nl)	217 ± 63	204 ± 57
Fibrinogen (mg/dl)	393 ± 143	370 ± 142
Hemoglobin (g/dl)	12.5 ± 1.9	12.1 ± 2
Postoperative laboratory values		
INR	1.29 ± 0.18	1.30 ± 0.18
PTT (s)	39 ± 7	39 ± 15
Platelet count (/nl)	183 ± 58	186 ± 51
Fibrinogen (mg/dl)	309 ± 125	330 ± 127
Hemoglobin (g/dl)	9.8 ± 1.7	9.6 ± 1.7
Postoperative complications	25 (35)[§]	28 (64)[§]
Favourable outcome (3 mo, mRS 0–3)	19 (27)[#]	3 (7)[#]

Values represent number of patients unless otherwise indicated (%). Means are given with SDs

DC decompressive craniectomy, *ASA* acetylsalicylic acid, *RBC* red blood cells, *FFP* fresh frozen plasma, *INR* international normalized ratio, *PTT* partial thromboplastin time, *mo* months, *mRS* modified Rankin scale

[†] $p = 0.0009$, OR 8.5, 95 % CI 2.2–32.2

[‡] $p = 0.01$, OR 11.1, 95 % CI 1.3–95.3

[§] $p = 0.004$, OR 3.2, 95 % CI 1.5–7.1

[#] $p = 0.008$, OR 4.9, 95 % CI 1.4–18

Neurological outcome

Favourable outcome was achieved in 12 patients without IVT prior to DC vs. ten patients with IVT prior to DC (19 vs. 19 %; $p = 1.0$). Furthermore, favourable outcome was achieved in three patients suffering from postoperative bleeding complications vs. 19 patients without (8 vs. 24 %; $p = 0.04$, OR 3.6, 95 % CI 1–13.2). Three of 44 patients with preoperative ASA therapy achieved favourable outcome compared to 19 of 71 patients without ASA medication prior to DC (7 vs. 27 %; $p = 0.008$, OR = 4.9, 95 % CI 1.4–18).

Multivariate analysis

We performed a multivariate logistic regression analysis of those variables that had been discussed to have any association on postoperative complications and outcome. In a

first multivariate regression model we analyzed factors influencing the rate of postoperative complications in patients with and without IVT for AIS. The variable "preoperative antiplatelet therapy with ASA" was the only significant and independent predictor for postoperative bleeding complications ($p = 0.002$, OR 3.9, 95 % CI 1.6–9.3; Nagelkerke's $R^2 = 0.15$).

In a separate analysis we analyzed factors influencing unfavourable outcome in patients with and without IVT for AIS. Age, gender, vascular risk factors, etiology of stroke, infarct location, laboratory data before and after DC, duration of DC procedure, postoperative bleeding complications as well as preoperative antiplatelet therapy with ASA were not significantly associated with unfavourable outcome. Additionally, IVT was not identified as independent predictor for unfavourable outcome (Nagelkerke's $R^2 = 0.26$).

Discussion

In the present series, we analyzed the management of patients without and with IVT prior to decompressive craniectomy due to cerebral infarction. Previously, small case studies stated that DC after thrombolytic treatment might be safe [9, 23]. However, symptomatic intracranial hemorrhage has been reported in up to 6 % of patients with IVT [5, 6, 8]. Furthermore, major bleeding complications have been reported in patients with craniotomy after intra-arterial thrombolysis [10]. In the present series with a large cohort of 115 patients with AIS, patients with IVT prior to DC suffered significantly more often from overall postoperative complications compared to patients without IVT prior to DC in the univariate analysis ($p = 0.03$, OR 2.4, 95 % CI 1.1–5). However, we found no increased risk for serious postoperative bleeding complications with the necessity for surgical intervention in patients with IVT prior to DC.

Thrombolytic therapy and its reversal

In the presence of fibrin, rtPA promotes the activation of plasminogen and, therefore, fibrinolysis [24]. Hence, IVT induces a coagulopathy, which might facilitate bleeding complications after surgery.

Hemostatic changes induced by rtPA have previously been verified to last for up to 72 h after treatment [25]. In the present series, therefore, DC has been performed within a critical time frame of rtPA-induced balance shifts between coagulation and fibrinolysis (mean time from IVT to DC: 45 h). Therefore, in some cases rigorous reversal of the thrombolytic effects caused by rtPA was deemed necessary. In the present series, RBC transfusion, platelet and FFP substitution were used as hemostatic and transfusion therapy to reverse coagulopathy and anemia. Unfortunately, neither prophylactic substitution strategies to reverse rtPA-induced coagulopathy nor guidelines to prevent possible thrombolysis-associated perioperative complications have yet been established based on class-I-evidence and, therefore, still remain controversial.

Influence of IVT on postoperative complications

In the present series, no increased risk for serious postoperative bleeding complications was detected in patients with IVT prior to DC compared to patients without IVT ($p = 0.3$). Furthermore, there was no significant difference in preoperative laboratory values and therefore, the number of patients who received perioperative application of hemostatic therapy in order to improve coagulopathy did not differ significantly between both groups. Additionally, previous studies with a small number of patients found no increased risk for postoperative complications of DC after IVT [9, 23]. Therefore, optimal perioperative management seems essential in these severely ill patients.

Influence of preoperative antiplatelet therapy with ASA on postoperative bleeding complications

The effect of previous and ongoing ASA treatment on the risk of ICH after IVT in patients with stroke is controversial [26–28]. A recent trial investigating possible beneficial effects of rtPA and early additional application of ASA was prematurely terminated due to an increased risk for ICH in the ASA group [29]. In our series, 38 % of the patients received ASA as antiplatelet therapy before onset of AIS. Furthermore, combination of ASA use before stroke and rtPA has been suggested to increase risk of severe hemorrhagic transformations [30–32]. Therefore, frequency of preoperative ASA intake was analyzed in the present series and did not differ significantly between patients with and without IVT prior to DC. Though, especially coexisting cardiovascular medication is frequent in patients suffering from AIS [26]. This might influence pharmacokinetics and might enable possible drug interactions. However, no specific drug interactions between ASA and rtPA causing alteration of the medical effect of rtPA on thrombolysis are currently known [33]. Preoperative laboratory values did not differ significantly between patients without or with ASA treatment prior to DC. However, in patients without ASA treatment, postoperative laboratory values including hemoglobin, fibrinogen and platelet count were significantly decreased compared to preoperative laboratory values. Furthermore, in patients with ASA treatment postoperative PTT, platelet count, and fibrinogen values did not differ significantly from preoperative

laboratory values. This might be explained by a significantly higher rate of platelet transfusion ($p = 0.0009$, OR 8.5, 95 % CI 2.2–32.2) and other hemostatic therapy ($p = 0.01$, OR 11.1, 95 % CI 1.3–95.3) in patients with ASA treatment prior to DC. In univariate analysis, the preoperative use of ASA as antiplatelet therapy was associated with a significantly higher rate of postoperative bleeding complications ($p = 0.0003$, OR 4.5, 95 % CI 2.0–10.2). Furthermore, in the multivariate analysis, the variable "preoperative antiplatelet therapy with ASA" was the only independent predictor for postoperative bleeding complications ($p = 0.002$, OR 3.9, 95 % CI 1.6–9.3). A recent randomized study reported a reduced rate of postoperative hemorrhage after platelet transfusion in patients with ASA therapy and emergency craniotomy for hematoma removal [34]. Therefore, cautious perioperative management is necessary in patients with known preoperative intake of antiplatelet drugs prior to DC, especially because the drug effect lasts longer in ASA compared to rtPA.

Neurological outcome

Patients with previous ASA medication suffered significantly more often from postoperative bleeding complications. Therefore, favourable outcome was significantly more often achieved in patients without ASA medication prior to DC compared to patients with ASA medication prior to DC ($p = 0.008$). However, ASA medication prior to DC was not identified as a predictor for unfavourable outcome in the present multivariate analysis.

Limitations

The main limitation of our study is its retrospective design. Patients were not randomized and, therefore, selection bias is possible. Furthermore, these results represent only a single-center experience. However, our standardized surgical approach and the large number of patients may outweigh some of these shortcomings.

Conclusions

DC in patients with IVT due to AIS is feasible. IVT was neither a predictor for bleeding complications, nor for outcome in patients undergoing DC. Therefore, DC should not be omitted in patients with space occupying infarction and IVT, but careful perioperative management is necessary. However, patients with or without IVT prior to DC suffered significantly more often from postoperative bleeding complications if antiplatelet therapy was applied before onset of AIS.

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard This study was conducted according to the standards of the local ethics committee.

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