Comparison of Hemostatic Profiles in the Intraoperative Volume Therapy with Human Albumin, Hydroxyethyl Starch (HES) and Autologous Fresh Frozen Plasma (FFP)

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Summary

Objective: In a prospective randomised study the effect of intraoperative infusions of 6% hydroxyethyl starch 200/0.5 (HES 200/0.5), 5% human albumin and autologous fresh frozen plasma (FFP) on coagulation parameters were investigated.
Methods: 33 (3x11) patients with hip replacement operation were included after collection of 3 autologous blood donations and one plasmapheresis. During the operation every patient received one of the colloidal solutions or autologous FFP for volume replacement up to 20 ml/kgBW. Before surgery, one hour after, and on the first postoperative day coagulation parameters (fibrinogen, PT, a-PTT, thrombin time, factor V, factor VIII, AT III) and the platelet aggregation were determined. Also hemoglobin, hematocrit and blood counts were made.
Results: A significant decline of factor VIII levels was found one hour postoperatively in the group with 6% HES 200/0.5, but it never lead to an increase of bleeding risk and compensated on the first postoperative day. Furthermore the blood loss was highest in the group with FFP.
Conclusion: The proportion of clotting factors in autologous FFP has no clinical benefit when administered intraoperatively instead of volume substitutes. The intraoperative volume replacement with 6% HES 200/0.5, given in moderate dosages, has no clinically relevant colloid-specific influence on hemostasis.

Keywords: hydroxyethyl starch, fresh frozen plasma, human albumin, coagulation, hip surgery, volume replacement

Introduction:

Today hydroxyethyl starch (HES) is used as a cost effective alternative to human albumin in isovolemic and normovolemic hemodilution, for the priming in extracorporeal circulation, the therapy of hemorrhagic shock and intraoperative volume therapy [1,2,3,4,5]. A further indication is the treatment of microcirculation disorders [6,7,8].

Besides adequate amount and duration of the volume effect the main goal for an optimal volume replacement solution is the minimization of side effects. Perioperative use of HES was combined sometimes with bleeding complications [9,10,11,12,13], whereas anaphylactic/anaphylactoid reactions seem to be extremely rare [14,15]. Pruritus, which is mostly related to long-term treatment with high dosages of HES, plays almost no role - or only a minor role - in volume replacement situations [16,17], observations to the contrary need to be considered with caution [18,19,20].

So far, HES with a molar substitution of 0.5 and a mean molecular weight (weight average molecular weight Mw) of 200000 (HES 200/0.5, similar to pentastarch) has less effects on clotting than high molecular HES with higher molar substitution (e.g. HES 450/0.7 or hetastarch) [21,22] The perioperative application of HES 200/0.5 is considered to be safe especially if the infused amount does not exceed 2 g/kgBW [15,23,24,25].

The main objective of this study was to compare the perioperative hemostatic profiles in volume replacement with three different solutions:
6% HES 200/0.5, which has known influences on coagulation parameters [26,27],
5% human albumin, which was hypothesized to have almost no influences or at least minor influences on coagulation parameters than HES 200/0.5 [5,28],
FFP, which was thought to counteract hemodiluting effects by a continuous supply of coagulation factors.
This study was considered to allow differentiations between typical influences of operation (FFP), hemodilution (human albumin) and artificial colloid (HES 200/0.5).

Methods

Study Design:
The prospective randomised study included 33 patients with hip replacement in the age of 41 to 71 years. Within 5 weeks prior to the operation date autologous

blood donations were performed with the aim to collect 3 units of packed red cells and 3 units of FFP. Additionally 600 ml FFP were collected by plasmapheresis.

A cement-free Zweimüller hip prosthesis was implanted during the operation, which was performed in spinal anesthesia. The patients were transfused intra- and postoperatively with autologous packed red cells to obtain a minimum hemoglobin level of 10 mg/dl. Prior to the operation 1000 ml Ringer´s lactate were given to compensate the relative loss of volume caused by spinal anaesthesia. Infusions with 6% HES 200/0.5, 5% human albumin or FFP were administered as exclusive colloidal solution in a maximum dosage of 20 ml/kgBW corresponding to the patient´s group. Ringer´s lactate was added as a non-colloidal component. The general aim was to keep the mean arterial pressure in a range of +/- 10% of the values prior to the operation.

Inclusion and Exclusion Criteria:
From all patients informed consent was obtained. The study was accepted by the local ethics committee. Patients with hemorrhagic disorders, portal hypertension, active malignant diseases, agranulocytosis, thrombopenic purpura and aplastic anemia, and those, who received an anticoagulation or had a too low hemoglobin-level (less than 11.5 mg/dl) or who could not complete the autologous blood donations were excluded from participation.

Group Allocation and Examination Points:
According to a randomisation table, 11 patients from group A were infused exclusively with 6% HES 200/0.5 (ISOHES®, Laevosan GmbH, Linz, Austria) and 11 patients from group B with 5% human albumin (Human Albumin, Immuno AG, Vienna, Austria). Patients in group C were transfused with autologous plasma and received no other colloidal infusion.

At three examination points blood was drawn for analyses. The examination point E1 was prior to spinal anaesthesia, E2 one hour after the end of the operation, and E3 on the first postoperative day. From these blood samples, blood counts, the determination of PT, a-PTT, thrombin time, factor V, factor VIII, AT III, and platelet aggregation under the induction of ADP, adrenaline and collagen were performed. The blood loss in suction units and drains was measured intra- and postoperatively.

Laboratory Methods:
An Amelung KC-4 device was used to perform clotting tests for the measurement of a-PTT (Pathromtim®, Behring, Marburg, Germany), PT (Thromborel S ®, Behring, Marburg, Germany) and thrombin time (Thrombin

Reagent, Boehringer Mannheim, Mannheim, Germany). Fibrinogen was tested on this device according to the Clauss-method (Multifibren®, Behring, Marburg, Germany). AT III was determined on a Hitachi 705 (Boehringer Mannheim, Mannheim, Germany) by using a chromogenic substrate method (Antithrombin III). Clotting tests and activity tests with a Behring Coagulometer were made to determine factor VIII concentrations (Factor VIII Deficiency Plasma, Baxter, Deerfield, IL, USA). Platelet aggregation methods were based on the protocol developed by Born and performed on a Dai-ichi device using ADP, collagen and adrenaline induction (Cluster ® Platelet Aggregation Reagents, Baxter, Deerfield, IL, USA).

Biometrics:
The homogeneity between the groups at baseline as well as the occurrence of significant differences between the treatment schemes were tested with a chi-square homogeneity test for nominal parameters and with an analysis of variance for metric parameters. For parameters showing a strong deviation from normal distribution (Kolmogorov-Smirnov test with Lilliefors significances) or a heteroscedasticity of variance (Levene test) a Kruskall Wallis one-way ANOVA was performed.
Multiple comparisons between the groups were made with Tukey's honestly significant difference test, because all groups had identical sizes. Using the Kruskall Wallis one-way ANOVA, analogous multiple comparisons according to Diehl and Kohr were calculated.

The changes in each parameter within each group were statistically determined with Wilcoxon's signed rank test (for ordinal parameters or in case of an extreme deviation from normal distribution) or by means of the two-sample t test for dependent samples. The confidence level was significant at 95% or highly significant at 99%. As no α-adjustment was made, the results are to be considered as purely descriptive.

Results:

Total Protein, Fibrinogen, AT III, Factor V and Factor VIII (table 1):
Total protein declined significantly within group A between the examination points E1 and E2 and reached at E3 a small rise. The intraoperative decline of fibrinogen was significant in the groups A and B. The AT III loss between E1 and E3 was highly significant in all groups, but the groups did not differ significantly at any time. The decline of factor VIII concentrations was highly significant in group A, and the difference between the groups A and B was highly significant at E2, a fact which can be influenced or caused by the higher

starting levels in the group B. Interestingly the factor VIII concentrations at E3 in the groups A and C were nearly the same. Different factor V concentrations were not significant within and between the groups at any time.

PT, a-PTT and Thrombin Time (table 1):

The PT-levels showed no significant differences at any point of examination between the groups. A highly significant reduction was seen within the groups A and B between E1 and E2 and between E2 and E3 in the groups B and C. Neither within nor between the groups significant differences of the a-PTT values were detected. The thrombin time decreased significantly between E1 and E2 in group A.

Table 1:
Values of PT, a-PTT, Thrombin Time, Fibrinogen, Factor V and Factor VIII

		E1				E2				E3			
	Group	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD
PT (%)	A	75.00	100	95.91	7.6	82	90	86.91	2.88	74	100	85.64	9.03
	B	85	100	93.64	5.75	74	95	87	7.22	65	100	81.91	9.34
	C	83	100	95.91	6.06	80	100	92.6	6.11	71	96	81	8.26
a-PTT (sec)	A	30	41	36.36	3.07	31	45	39.18	4.24	35	41	37.09	1.87
	B	32	39	34.18	2.18	32	38	35	2.28	31	44	36.73	3.61
	C	33	38	36.09	1.87	31	38	35.8	2.25	35	43	37.73	2.2
Thrombin. Time (sec)	A	18	20	19.09	0.7	15	20	17.45	1.29	16	20	17.82	1.25
	B	17	20	19	1.41	17	21	19.36	1.43	15	22	18.82	2.32
	C	18	20	18.91	0.83	16	20	19.1	1.29	18	21	19.18	0.87
Fibrinogen (mg/ml)	A	183	418	252.82	62.63	146	316	206	50.06	220	418	301.09	68.73
	B	195	337	260.73	42.11	162	306	210.09	38.75	230	356	290.82	37.45
	C	200	343	261.45	47.81	180	340	247.3	59.13	242	420	315.18	55.28
Factor VIII (%)	A	74	140	102.82	20.21	52	140	86.09	28.45	89	170	131.73	23.38
	B	91	190	136.45	28.83	84	180	127.09	33.9	105	200	145.45	26.98
	C	84	135	107.18	19.07	68	135	96	27.27	107	155	126.36	14.08
Factor V (%)	A	73	120	87.64	13.6	46	105	68.55	15.16	64	96	78.73	9.76
	B	60	198	97	38.48	48	105	72.91	19.03	53	125	83.64	22.01
	C	59	112	87.18	16.58	60	88	71.9	9.06	64	100	80.09	12.19
AT III (%)	A	83	110	95.91	8.3	56	88	72.82	8.94	69	94	79.18	8.29
	B	78	127	93.18	12.74	66	85	75.09	6.01	58	100	76.18	11.11
	C	70	112	92.82	12.47	68	102	84.2	9.46	60	87	78.45	8.47

Hematocrit, Hemoglobin, Erythrocyte Counts (table 2):

As expected, the hematocrit- and hemoglobin-levels were lowered during the operation. The starting levels were comparable. The hemoglobin- and hematocrit-reduction was highly significant in group C between the examination points E2 to E3. However, the differences between the groups were not significant. The postoperative loss of erythrocytes was also highly significant within group C.

Platelet and Leucocyte Counts, Platelet Aggregation (tables 2 and 3):
The leucocyte and platelet counts were not significantly different between the groups and also within the groups. The analysis of the endpoints of the platelet aggregation showed no significant difference under the mentioned inductions.

Table 2:
Values of Total Protein, Platelets, Erythrocytes, Leucocytes, Hemoglobin and Hematocrit

		E1				E2				E3			
	Group	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD
Total - Protein (g/l)	A	48	68	60.82	5.81	34	54	46.36	5.75	38	57	47.91	6.49
	B	57	74	63.82	5.13	47	68	56.36	5.77	47	64	55.36	4.86
	C	55	69	63.18	4.69	47	66	56.6	5.72	45	70	55.55	7.01
Platelets (G/l)	A	187	329	241.36	49.96	149	266	212.27	40.76	136	276	202.73	42.86
	B	166	337	233.73	45.56	132	266	200.36	37.01	106	239	181.91	40.81
	C	179	335	261	51.17	144	253	199.9	39.46	134	234	182.36	36.31
Leuco-cytes (G/l)	A	3.38	9.04	5.32	1.81	4.73	18.53	8.83	4.14	5.33	15.58	9.11	2.8
	B	3.38	6.46	4.93	0.97	5.51	16.98	9.53	3.72	5.43	11.65	7.68	1.76
	C	3.57	15.65	6.33	3.32	7.75	28.23	11.19	6.17	5.98	22.52	9.34	4.68
Hemo-globin (g/100ml)	A	10	15.4	11.75	1.6	9	13.6	11.27	1.57	8.5	14.3	11.06	1.54
	B	10.3	14.8	12.65	1.25	9.7	13.4	11.6	1.18	8.8	13.3	11.34	1.28
	C	10.7	14	12.79	1.21	8.6	12.8	10.91	1.38	9	13.5	10.62	1.32
Hemato-crit (%)	A	30.2	44.1	35.08	4.23	26.5	39	33.36	4.29	24.5	40	31.85	4.35
	B	31	44.4	37.16	3.51	28.8	39.7	34.01	3.47	25.5	38.8	33.02	3.79
	C	31.3	45.1	37.49	4.01	25.4	37.5	31.65	3.94	26.4	39.4	31.39	3.74
Erythro-cytes (T/l)	A	3.29	4.64	3.77	0.42	2.87	4.27	3.62	0.45	2.81	4.25	3.51	0.46
	B	3.5	4.77	4.11	0.38	3.16	4.44	3.76	0.37	2.89	4.4	3.69	0.39
	C	3.46	4.96	4.08	0.42	3.03	4.11	3.54	0.41	2.73	4.29	3.42	0.47

Table 3:
Maximum Time of Platelet Aggregation Values under Induction of ADP, Adrenaline und Collagen

		E1				E2				E3			
	Group	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD
ADP (sec)	A	200	293	248.91	33.19	130	292	252.73	44.25	212	291	257.36	26.07
	B	159	299	232.36	48.56	208	292	263.18	25.41	207	292	260.91	31.22
	C	147	293	249.36	50.13	189	298	255.6	33.68	181	291	251.73	40.04
Adrenaline (sec)	A	207	298	261.73	33.23	154	299	272.8	44.17	189	298	278.73	30.94
	B	220	296	265.09	30.02	255	298	282	15.82	231	297	269.36	21.04
	C	113	296	252.09	53.19	145	299	250.8	50.83	252	299	283.82	16.36
Collagen (sec)	A	214	296	268.64	26.2	149	295	250.27	41.07	182	290	247.82	30.57
	B	141	295	260.73	43.07	146	294	251.8	41.96	200	299	264.09	31.81
	C	184	298	244.36	40.53	236	298	272.7	22.07	234	296	273.73	20.15

Intraoperative Consumption of Blood Components, Infusion Volumes and Operation Time (table 4):

The mean operation time, which is a main determinant of the blood loss, did not differ significantly between the groups (group A: 69.45 min; group B: 71.82 min; group C: 73.91 min). The mean intraoperative consumption of FFP was in group C 972.73 ml, the volume of HES infused in group A was 731.82 ml and human albumin in group B 613.64 ml. The use of non-colloidal infusions was not significantely different between the groups (group A: 3011 ml; group B: 3511 ml; group C: 3482 ml).

Table 4:
Infusions, Transfusions and Blood Loss

		intraoperative (E1 - E2)				postoperative (E2 – E3)			
	Group	min	max	$\bar{x}$	SD	min	max	$\bar{x}$	SD
Non-Colloidal Infusions (ml)	A	0	4000	2136.40	1097.52	0	1000	875	353.5
	B	1500	4500	2636.36	951.08	0	1000	875.14	377.96
	C	1500	4000	2545.45	907.04	0	1500	937.5	417.26
Packed Red Cells (ml)	A	0	1100	631.82	295.2	0	500	100	192.72
	B	0	900	386.36	339.18	0	300	42.86	113.39
	C	400	1500	727.27	322.77	0	900	112.5	318.2
Colloidal Infusions (ml)	A	500	1500	772.73	343.78				
	B	250	1000	613.64	282.04				
	C	400	1500	972.73	388.18				
Blood Loss (ml)	A	150	850	486.36	196.33	100	950	507.14	359.89
	B	300	900	527.27	179.39	150	500	316.25	114.88
	C	400	1300	675.45	344.42	190	1200	510	363.43

The mean use of packed red cells was highest in group C with 839.77 ml followed by group A with 731.82 ml and group B with 429.22 ml, the difference between the groups C and B was highly significant. Similar results were found for the total blood loss, which was highest in group C with 1185.5ml followed by group B with 993.5 ml and group A with 843.5 ml.

Discussion:

6% HES 200/0.5 is a colloidal solution, which is commonly infused at intraoperative volume deficiencies [29,30]. The use of 5% human albumin is nowadays restricted more and more to situations with a special need for this natural colloid, which is expensive and does not have relevant advantages to

artificial colloids in most cases [31,32]. Autologous FFP is a split product of preoperative collections and is primarily designated for the substitution of clotting factors [33].

The pharmacokinetic properties of HES depend on the amount and the pattern of substitution with hydroxyethyl groups, the mean molecular weight plays only a minor role. HES molecules with a high degree of substitution and a high portion of glucose units with hydroxyethylation at the C2-position (high C2/C6 substitution ratio) are less degradable by α-amylase and hence tend more to accumulation [34,35]. Most reports of coagulation disorders in connection with HES concern high dosage and/or long-term application of high-molecular and highly substituted types of this colloid (e.g. HES 450/0.7 or hetastarch) [36,37,38,39,40]. Treib and coworkers found that the accumulation of high-molecular HES fractions in blood correlates with the impairment of the intrinsic clotting system, especially with the decrease of factor VIII activity [41,42].

In-vivo and in-vitro-investigations showed, that HES inhibits the endothelial activation in an early phase and that this mechanism is responsible for a dose-dependent reduction of the release of von Willebrand factor [26,43].

In our study a slightly higher reduction of factor VIII activity in the intraoperative phase happened in group A (6% HES 200/0.5) compared with group B (5% human albumin), whereas group A and group C (FFP) showed almost identical courses. However, the observed reductions of factor VIII activity were not distinct enough to induce any clinical risk. As a matter of fact no single patient included in the study reached a coagulation status, which was to be interpreted as a risk for bleeding complications. The decrease of factor VIII activity was always over-compensated in the postoperative phase, a fact which was also seen with fibrinogen. Similar to findings on healthy volunteers [27] intraoperative infusion of HES 200/0.5 influenced factor VIII activity more than human albumin, but interestingly not more than FFP. These results indicate on the one hand, that the operative situation is not too heterogeneous for the determination of even slight coagulation effects, and on the other hand, that substitution of moderate amounts of blood loss with autologous FFP obviously fails to improve the hemostatic profile.

The low clinical relevance of 6% HES 200/0.5 influence on coagulation was also documented by tendencies of higher need for infusions and of higher blood loss in group C (FFP).

There are reports, that HES 200/0.5 may inhibit platelet function [44,45], although also opposite findings (especially under perioperative conditions) are

published [5,24]. In our study the examinations on platelet function did not show any differences between the groups.

It was surprising that the transfusion of autologous FFP in the intraoperative phase was not endowed with beneficial effects. Although the total protein levels stayed constant, no significant difference was found in the factor VIII, factor V and AT III concentrations as well as in the PT and a-PTT levels. Taking into consideration the tendency of this group to a higher blood loss and higher infusion volumes, we come to the conclusion, that the application of autologous FFP in intraoperative situations with mild to moderate volume deficiency has no benefit for the patient - even from a hemostasiological point of view. However, the cause of the elevated blood loss in group C (FFP) needs further investigations. A possible explanation might be a marked counteraction of specific inhibitors of certain clotting factors.

In the view of the above mentioned results, the therapy with 6%HES 200/0.5 is clinically safe, although slight factor VIII activity reductions are detectable. Concerning the risk for hemostatic impairment, neither the additional application of clotting factors by FFP nor the substitution of natural colloids by 5% human albumin has clinically relevant advantages to the volume replacement by 6% HES 200/0.5 at dosages up to 20 ml/kgBW. However, recently a new type of HES (HES 130/0.4) is available, which influences hemostasis even less than HES 200/0.5 [46,47,48].

Conclusion:

The proportion of clotting factors in autologous FFP has no clinical benefit when administered intraoperatively instead of volume substitutes. The intraoperative volume replacement with 6% HES 200/0.5, given in moderate dosages, has no clinically relevant colloid-specific influence on hemostasis.

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