The effect of acute normovolemic hemodilution and acute hypervolemic hemodilution on coagulation and allogeneic transfusion

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ABSTRACT

Objective: In this study, acute normovolemic hemodilution (ANH) and hypervolemic hemodilution (HHD) were compared with no hemodilution with regards to the effectiveness in blood usage and coagulation parameters.

Methods: The study was performed from February to August 2001 at Hacettepe University Hospital, Ankara, Turkey. Thirty patients undergoing hip arthroplasty surgery were prospectively randomized into: ANH group [autologous blood 15 mL kg^{-1} was withdrawn and replaced by 6% hydroxyethylstarch (HES)] or HHD group (HES was administered without removal of any autologous blood) or the control group (no hemodilution). In all groups, blood was given when hemoglobin concentration was <9 g dl^{-1}.

Results: Three groups were clinically similar regarding blood loss, mean arterial pressures and coagulation parameters. But allogeneic transfusion requirements were significantly less in hemodilution groups (20% in ANH, 40% in HHD) compared to the control group (100% of patients).

Conclusion: We conclude that hemodilution (both ANH and HHD) decreases the demand for homologous blood without adversely affecting hemodynamics or coagulation parameters and HHD seems to be a simple and valuable alternative to ANH in orthopedic patient undergoing hip replacement.

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Allogenic blood transfusion is more immunosuppressive and associated with the risk of postoperative infections and transmission of viral diseases, compared to autologous blood transfusion.[1-3] Several blood conservation strategies have been introduced with the aim of reducing allogenic blood transfusion. Per operative autologous blood donation, meticulous (a sanguineous) surgical technique, intra and postoperative salvage of the patients blood and its' transfusion and acceptance of lower hemoglobin level have been used to avoid homologous blood donation.[4,5]

The acute normovolemic hemodilution (ANH) is a technique that comprises the removal of whole blood from a patient along with the restoration of circulating blood volume with cellular fluid shortly before an anticipated significant surgical blood loss simultaneously with infusion of crystalloid or colloid solutions. Blood is collected in standard blood bank bags containing citrate anticoagulant.[6] This technique was simplified by hemodiluting the patients with hydroxyethylstarch preoperatively without removing their autologous blood, resulting in a hypervolemic hemodilution.[7] The aim of this study was to compare ANH and hypervolemic hemodilution (HHD) with no hemodilution regarding the blood loss, hemodynamic changes, coagulation parameters and transfusion requirements in patients undergoing hip arthroplasty surgery.

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Methods. After obtaining approval from the Human Ethics Committee of the university and patient informed consent, we studied 30 patients undergoing hip arthroplasty surgery at Hacettepe University Hospital, Ankara, Turkey from February to August 2001 . Exclusion criteria were American Society of Anesthesiology class III, hemoglobin (Hb) concentration <12 gr dl^{-1}, renal insufficiency (creatinine concentration >1.5 mg dl^{-1}), liver dysfunction (aspartate aminotransferase/gamma glutamyl transferase >40 IU $litre^{-1}$, alanine aminotransferase/alkaline phosphatase >40 IU $litre^{-1}$), coagulation abnormalities (platelet count <100 x 10^9 L^{-1}, activated partial thromboplastin time (aPTT) >40 s), medication with acetylsalicylic acid or other cyclooxygenase inhibitors within 10 days of surgery, untreated hypertension, clinically indent limitations of cardiac or pulmonary functions.

Patients were randomly divided into 3 groups by sealed envelope assignment; Group ANH (n=10), Group HHD (n=10) and control group; Group control normovolemic (CNV) (n=10). The patients were premedicated with oral (po) diazepam 10 mg approximately 2 hours before anesthesia induction. Patients were monitored with pulse oximetry and 3 lead electrocardiogram (ECG) and radial arterial catheter was inserted for continuous monitoring of arterial blood pressure (BP) and central venous catheter was inserted for monitoring central venous pressure (CVP). Anesthesia was induced in 3 groups with, thiopental 5 mg kg^{-1}, fentany l2 mg kg^{-1}. Tracheal intubations were facilitated with intravenous vecuronium bromide 0.1 mg kg^{-1}. Anesthesia was maintained with 60% nitrous oxide in 0_2 supplemented with 1.5-2% sevoflurane.

Immediately after induction of anesthesia, hemodilution was performed. In the ANH Group 15 ml kg^{-1} autologous blood was removed from a peripheral vein and stored in units of approximately 400 ml with citrate, phosphate, dextroze, alanine (CPDA)-1 stabilizer. Simultaneously, an equal amount of hydroxyethylstarch (HES) (6%) (15 ml kg^{-1}) was given via separated venous line in the contra lateral arm. In the HHD Group 15 ml kg^{-1} of HES was infused at a rate of 70 ml min^{-1} using rapid infusion pump. In this group no blood was removed. In the control group, no hemodilution with HES was performed. For the intraoperative volume therapy, only lactated Ringer's solution was used. The autologous blood was retransfused after the implantation of the hip prosthesis or at the end of the operation in the ANH group. If necessary, (Hb < 9 g) homologous blood was also transfused in all groups.

Intraoperative blood loss was measured by weighing sponges and calculating suctioned blood. Hemoglobin, hematocrit (htc), Platelet and coagulation variables (prothrombin time (PT), aPTT, central venous pressure (CVP), heart rate were measured at the following times: preoperatively (baseline), after hemodilution, immediately after the operation, 24 hour after the operation.

Statistical analysis of the data was undertaken by parametric and nonparametric methods after distribution of data had been evaluated by Kolmogorov-Smirnov test. Chi-square test was used for comparison of gender and the number of patients requiring allogeneic blood among the groups. Kruskal-Wallis test was used for comparison of age, height, weight, duration of operation, intraoperative blood loss, postoperative drainage, amount of homologous blood transfusions, and intraoperative crystalloid infusion among groups. Repeated measures of variance analysis were used for analyzing hematocrit, hemodynamic parameters and coagulation tests among groups and within time. Data were expressed as median (95% CI) and ($p<0.05$) was considered significant. When significance was noted in data, Mann-Whitney U test was performed for post-hoc comparisons with correction of significance values.

Results. The 3 groups were similar regarding age, gender, height weight, duration of operation, intraoperative blood loss, postoperative drainage and the amount of intraoperative crystalloid infused (**Table 1**) ($p>0.05$).

Although the blood loss (both intraoperative and postoperative) was comparable between the 2 hemodilution groups and the control groups, the median number of red blood cell units transfused and the number of patients requiring blood transfusion were significantly lower in the hemodilution groups compared to the control group. One patient required one unit and another patient required 2 units of allogeneic blood in the ANH group. Three patients required one unit and one patient required 2 units of allogeneic blood in the HHD group. Whereas, 7 patients required one unit and 3 patients required 2 units of allogeneic blood in the control group during the operation when hemoglobin was lower than 9 g in percentage.

In the ANH group 1065 (975-1170) mL autologous blood was removed and replaced with HES. In the HHD group, 1020 (900-1275) mL of HES was administered. Hematocrit levels decreased significantly after hemodilution in the ANH and HHD groups (**Table 2**) (**Figure 1**). The postoperative hematocrit levels remained significantly lower compared to baseline values in all groups but there was no difference between groups ($p<0.008$ within group comparisons $p>0.05$ between groups).

Mean arterial pressure after hemodilution in the HHD group was significantly higher than the ANH group ($p<0.05$) (**Table 2**) (**Figure 2**). Within ANH

Table 1 - Patient characteristics, duration of operation, blood loss, and homologous packed red blood cells administration. Data is given as median (95% CI) (* - *p*<0.008 between ANH and the control groups and † - *p*<0.008 between HHD and the control groups)

Characteristics	**ANH group**		**HHD group**		**Control**		***p***
Gender (F/M)	8/2		8/2		8/2		0.99
Age (yr)	60.5	(56-63)	57.5	(53-65)	57.5	(53-65)	0.876
Height (cm)	164	(158-174)	163	(158-175)	164	(158-173)	0.828
Weight (kg)	71	(65-78)	68	(60-85)	68	(60-80)	0.548
Duration of operation (min)	105	(95-125)	102.5	(95-125)	105	(95-125)	0.795
Intraoperative blood loss (ml)	740	(600-830)	650	(500-855)	695	(510-855)	0.275
Postoperative drain	182	(145-260)	283	(112-370)	235	(112-330)	0.243
Homologous PRBC (Units)	0	(0-2)*	0	(0-2)†	1	(1-2)*†	0.003‡
Intraoperative crystalloid (mL)	1290	(1100-1375)	1300	(1250-1375)	1290	(1020-1375)	0.803

ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution, PRBC - packed red blood cells
‡ - compare ANH with control, F/M - female/male

group, the MAP decreased significantly after hemodilution but returned to baseline postoperatively (*p*<0.008). In the HHD and the control groups, the MAP values were lower than baseline after hemodilution, after completion of surgery and 24 hrs after the operation (*p*<0.008 for within group measurements). Postoperatively, mean arterial pressures in the ANH group were higher than the other 2 groups. The CVP in the HHD group was significantly greater than the other 2 groups after hemodilution but was lower than the other 2 groups postoperatively.

The platelets after hemodilution were lower in both hemodilution groups compared to the baseline values (*p*<0.008 within group comparisons) (**Figure 3**). Although the platelet counts initially decreased after hemodilution, they increased to baseline levels in the postoperative period in the ANH group and the control groups. The platelet count in the HHD group progressively decreased after hemodilution and was the lowest within the 3 groups on the first postoperative day (*p*<0.05 between groups).

Coagulation parameters also showed a dilution effect, but in HHD group this hemodilution effect was significantly higher than the ANH group (**Table 2**) (**Figures 4 & 5**). In the HHD group, aPTT and International normalized ratio (INR) increased after hemodilution (*p*<0.008 compared to baseline) and gradually returned to baseline values at the postoperative 24 hour measurements. At postoperative 24 hours value aPTT and INR values were similar in all groups (*p*>0.05).

Discussion. Blood loss is a serious complication of anesthesia and surgery. Patients who became anemic are weakened and frequently require transfusion of allogeneic blood, which is expensive and transmits disease.[3] Several blood conservation strategies have been introduced with the aim of reducing allogeneic blood transfusion. Acute normovolemic hemodilution and acute hypervolemic hemodilution are 2 blood conservation strategies using hemodilution.[1-3] In this study, we compared these 2 dilution methods with a control group for their efficacy in transfusion, hemodynamics and coagulation parameters. Intra and postoperative blood loss was almost identical in 3 groups and in the lower range of what has been reported in the literature.[8-10] Whereas, allogeneic transfusion requirements were significantly less in hemodilution groups (20% in ANH, 40% in HHD) compared to the control group (100% of patients). Both of the hemodilution groups were also effective in reducing the median number of blood units transfused. There was one unit difference between the hemodilution groups and the control group.

As their name implies, the 2-hemodilution methods differ regarding the blood volume after hemodilution. The safety of ANH depends on the maintenance of normovolemia. In all patients, care must be taken to match the continuos replacement of volume with removal of blood. In older patients and where cardiac disease may be suspected additional care is necessary. Bryson et al[11] used a metaanalysis to evaluate whether ANH was effective in reducing perioperative allogenic transfusion and suggested that although many studies reported an impressive reduction in blood transfusion, these reductions might be due to flawed study design. However, Mielke et al[12] has

Table 2 - Perioperative changes of hematocrit (Hct), platelet count (Plt), Prothrombin time (International Normalized ratio (INR)), activated partial thromboplastin time (aPTT) and mean arterial pressure (MAP) and central venous pressures (CVP). Data is given as median (95% CI) (* - $p<0.008$ between ANH and the control groups, † - $p<0.008$ between HHD and the control groups, ‡ -$p<0.008$ between ANH and HHD groups).

Perioperative changes	**ANH group**		**HHD group**		**Control**		***p***
Preoperative Hct (%)	39.2	(34.6-46.0)	41.1	(37-45.3)	43.2	(35.8-45.8)	0.5
Preoperative Plt (1000/mm³)	280	(132-367)	286	(240-387)	285	(240-387)	0.98
Preoperative INR	1.1	(0.92-1.3)	1.15	(0.95-1.4)	1.15	(0.92-1.14)	0.6
Preoperative aPTT (sn)	27.6	(26.4-35.9)	28.5	(26.8-32.1)	27.6	(26.4-32.1)	0.4
Preoperative MAP (mm Hg)	89.5	(76-97)	85.5	(75-95)	87	(70-97)	0.86
Preoperative CVP (mm Hg)	5.5	(4-8)	5.5	(5-8)	5.5	(4-8)	0.98
Posthemodilution Hct (%)	32.5	(26.8-38.5)‡	30.2	(28.5-31.3)†‡	41.7	(26.8-38.5)†	0.01§
Posthemodilution Plt (1000/mm³)	213.5	(110-298)	207	(178-312)	235	(199-312)	0.42
Posthemodilution INR	1.1	(1.02-1.29)‡	1.55	(1.4-1.8)‡	1.35	(1.1-1.8)	0.01§
Posthemodilution aPTT (sn)	27.3	(23.6-29.5)‡	35.9	(31.8-38.5)‡	32.2	(24.4-32.2)	0.000§
Posthemodilution MAP (mm Hg)	75	(65-85)‡	81	(72-90)‡	79.5	(72-87)	0.015§
Posthemodilution CVP (mm Hg)	8	(7-9)*‡	10	(9-11)‡	8.5	(7-11)*	0.000§
Postoperative Hct (%)	32.7	(26.5-38.6)	29.1	(26.5-38.6)	32.3	(26.5-38.6)	0.398
Postoperative Plt (1000/mm³)	258	(123-354)	204	(167-300)	241	(175-310)	0.96
Postoperative INR	1.2	(1.1-2.3)	1.4	(1.2-1.5)	1.35	(1.2-1.5)	0.052
Postoperative aPTT (sn)	26.75	(23.8-32.3)‡	33.8	(30.1-35.6)†‡	27.5	(24.7-34.2)†	0.01§
Postoperative MAP (mm Hg)	86.5	(82-97)*‡	79	(70-85) ‡	79	(70-87)*	0.04§
Postoperative CVP (mm Hg)	10	(9-11)‡	8	(7-9)†‡	9.5	(8-10)†	0.000§
Postoperative 24hr Hct (%)	32.7	(30.1-40.1)	34.9	(30.2-36.7)	32.9	(30-36.5)	0.89
Postoperative 24h Plt (1000/mm³)	283	(138-356)	195	(163-300)†	283	(190-356)†	0.010§
Postoperative 24h INR	1.2	(1.1-1.87)	1.2	(1.1-1.3)	1.2	(1.1-1.3)	0.68
Postoperative 24h aPTT (sn)	26.5	(24.7-30.1)	30.1	(24.7-34.2)	24.2	(24.2-34.7)	0.182
Postoperative 24h MAP (mm Hg)	80.5	(76-88)	76	(72-84)	80.5	(72-88)	0.106
Postoperative 24h CVP (mm Hg)	9	(7-10)‡	7	(6-8)†‡	9	(7-10)†	0.002§

ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution, PRBC - packed red blood cells
§ - compare ANH with NHD

concluded that ANH is most beneficial and potentially valid as a cost-effective alternative to preoperative autologous donation for healthy adults with high initial hematocrit and the capacity to tolerate dilution-induced anemia who are undergoing procedures associated with significant hemorrhage. Trouwborst at al[3] reported that HHD without removal of blood, which reduces loss of red blood cells, allowed major surgery to be completed safely without homologous transfusion. The HHD seems to be a simple as well as time-and cost-saving alternative for ANH in patients undergoing total hip replacement with a predicted blood loss of approximately 1000 mL. Trowborst et al,[3] also found that HHD makes a significant increase in pulmonary wedge pressure and pulmonary artery pressure but no clinical evidence of pulmonary edema. It is possible to administer an appropriate volume of colloidal solution to induce HHD without any adverse hemodynamic effects by using inhalation anesthetics (vasodilator effect of sevoflurane).[3] In our study, we used sevoflurane and followed the hemodynamics during general anesthesia and postoperatively. As expected, the

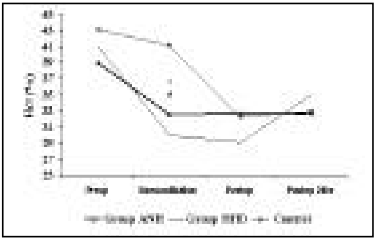

Figure 1 - Hematocrit levels in the 3 groups. (* - $p<0.05$ between groups, # - $p<0.008$ compared to baseline within group). ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution.

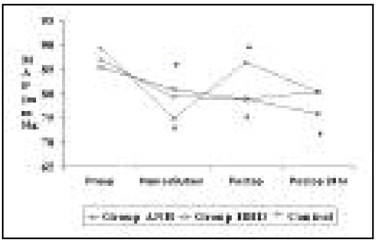

Figure 2 - The mean arterial pressures in the 3 groups. (* - $p<0.05$ between groups # - $p<0.008$ compared to baseline within group). ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution.

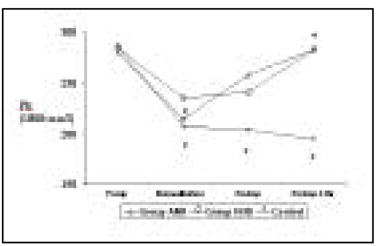

Figure 3 - The platelet counts in the 3 groups. (* - $p<0.05$ between groups # - $p<0.008$ compared to baseline within group). ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution.

mean arterial pressures and central venous pressures after hemodilution were highest in the HHD group among the 3 groups. Whereas, postoperative mean arterial pressures and CVP were highest in the ANH group when autologous blood was retransfused. Although, there were some statistical differences between and within the 3 groups regarding these 2 hemodynamic parameters, we thought those differences were clinically insignificant as mean arterial pressures and central venous pressures were almost always within clinically acceptable limits. It is shown that the use of starch solution for HHD did not result in excessively high arterial blood pressure and we could not find any signs of excessive intravascular volume after HHD.[5]

Singbartl at al[2] presented a clinically related, exactly calculated and independently validated mathematical model to evaluate and compare the efficacy of HHD, ANH and no hemodilution (HD): They found that HHD can not replace ANH to reduce or avoid homologous blood transfusions. Nevertheless, for surgical blood loss less than 40% of estimated blood volume HHD seems to offer some advantages over ANH and no HD, as it could help save red blood cell (RBC). Singbartl et al[2] also suggested that the operation that requires blood loss <2000 mL or 40% of estimated blood volume, HHD appears to be superior to ANH and no HD and should be considered first choice to save RBC. The HHD is easier, less time consuming and less expensive than ANH.[2] It should be noted that we compared ANH and HHD only in orthopedic patients undergoing hip replacement with an estimated blood loss of approximately 1000 mL.[14] Our results can not be generalized to include cases with larger blood losses.

Using HHD dilution (lowering hematocrit) of blood is solely achieved by preoperative infusion of a plasma expander without removal of autologous blood. Possible contamination of the autologous blood unites or accidental administration to a wrong patient, is avoided by this method.[3,13]

When plasma substitutes are used as the diluents for maintaining isovolemia, the influence on coagulation must be considered. In HHD, preoperative infusion volume and rate of HES was decided according to the report of Mielke et al.[12] The HES 6% (molecular weight 70 kDa, molar substitution 0.5) was chosen in our study for hemodilution due to its excellent safety record and intravascular retention.[3] Alternative colloid solutions include dextran, which sometimes causes allergic reactions, and lower percentage starch solutions, which are less useful.[14] Several studies on impaired homeostasis with increased bleeding tendency after the use of HES have been published.[5,7] The majority of these studies used the first generation high molecular weight HES (450 kDa, 0.7) and also resulted in the most pronounced

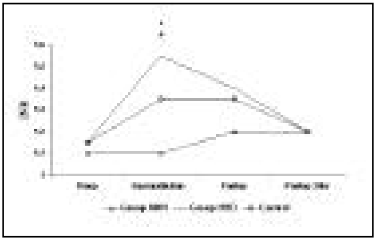

Figure 4 - The International Normalized ratio (INR) in the 3 groups. (* - $p<0.05$ between groups # - $p<0.008$ compared to baseline within group). ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution.

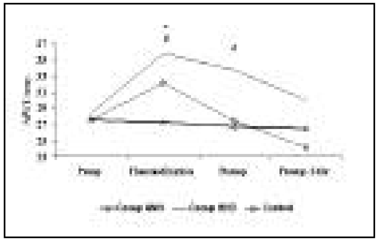

Figure 5 - The activated partial thromboplastin time (aPTT) in the 3 groups. (* - $p<0.05$ between groups # - $p<0.008$ compared to baseline within group). ANH - acute normovolemic hemodilution, HHD - hypervolemic hemodilution.

impairment of platelet aggregation. The medium molecular weight (200-270 kDa) HES preparations did not show the same negative effects on platelet functions. Low molecular weight (70 kDa) and medium molecular weight HES preparations with lower molar substitution (0.5) appear to be significantly less detrimental to coagulation and studies in humans have confirmed that these preparations can be used safely.[15] Also in our study, the changes in the coagulation parameters were clinically insignificant in hemodilution groups and the control group.

The predicted effect of retransfused sampled blood in ANH on coagulation and hemoglobin values seems to be partly overestimated, since there is an amount of the simultaneously administered starch in addition to the buffer and anticoagulant within the autologous blood unit. After retransfusion of autologous blood in the ANH group, except the increase in platelet count, we did not observe any differences between groups in aPTT or INR levels at the end of the operation. These results are consistent with the study of Mielke et al.[12] Remarkably, despite different study designs (namely, different degrees of hemodilution, inhomogeneous inclusion criteria), in most studies, including our investigation, only small changes in PT and aPTT after normovolemic hemodilution were observed. We did not find any study on the effect of HHD on coagulation parameters. Besides the type of colloid used, the hemodilution, itself, can result in an impairment of primary homeostasis and platelet dysfunction. Hemodilution implies dilution of all constituents of blood, including those responsible for coagulation. In addition, the increase in capillary flow resulting from the reduction in viscosity has the potential to increase oozing from large cut surfaces.[16] The blood losses in our study were similar in the 2-hemodiluted groups and the control group without hemodilution. We did not use blood salvage in our series and saw that homologous blood usage is higher than other studies with cell saver. Hemodilution is likely of greater benefit when a cell saver can not be used or is not available. The proportion of patients requiring homologous blood in our series was higher than other studies.[10,11,17]

We conclude that hemodilution (both ANH and HHD) decreases the demand for homologous blood without adversely affecting hemodynamics, blood loss or coagulation parameters. The HHD seems to be a simple and valuable alternative to ANH in orthopedic patient undergoing hip replacement.

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