


RESEARCH NOTE

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# Comparison of hydroxyethylstarch (HES 130/0.4) and 5% human albumin for volume substitution in pediatric neurosurgery: A retrospective, single center study

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## Abstract

**Objective:** Colloid solutions are commonly used to maintain perioperative fluid homeostasis. In regard to perioperative infant-centered care, data about the impact of colloids are rare. New data suggest a possible positive effect of hydroxyethyl starch (HES) concerning blood brain barrier. Therefore we conduct a retrospective single center study of children scheduled for neurosurgery, age < five with a blood loss > 10% of body blood volume, receiving either 6% HES 130/0.4 or 5% human albumin (HA).

**Results:** Out of 913 patients, 86 were included (HES = 30; HA = 56). Compared to HES [ $16.4 \pm 9.2$  ml/kg body weight (mean  $\pm$  SD)] HA group received more colloid volume ( $25.7 \pm 11.3$ ), which had more blood loss [HA  $54.8 \pm 45.0$ ; HES  $30.5 \pm 30.0$  (%) estimated blood volume] and higher fluid balances. Fibrinogen was decreased and activated partial thromboplastin time was elevated in HA group. Urinary output, creatinine and urea levels did not differ between the two groups. Serum calcium, total protein levels were lower in HES group. HA treated infants tended to have shorter ICU and hospital stays. We conclude that none of the investigated colloid solutions were without leverage to infants. Consequently randomized controlled trials about perioperative goal-directed fluid replacement of children undergoing (neuro)-surgery with major blood loss are needed.

**Keywords:** Hydroxyethylstarch, HES, Human albumin, Pediatric neurosurgery, Volume substitution, Colloid, Crystalloid

## Introduction

Despite numerous studies on perioperative fluid resuscitation, goal-directed fluid therapy (GDFT) remains a daily challenge during surgery. The choice whether to use crystalloids (CL) and/or synthetic or natural colloids (COL) stays controversial [1, 2]. Both hyper- and hypovolemia impairs the patient's outcome [2]. The comparability of

intravenous fluid management between different procedures, e.g. cardiac-, abdominal surgery or ICU, is limited. The number of available data about the impact of HES on children is very low compared to adults' HES is the most used synthetical colloid and it was established to replace albumin for many circumstances, e.g. for acute hemorrhage. The usage of HES was described as 'safe' for children [3], although in the recent summary of product characteristics („Fachinformation“) the usage of HES for children is still not recommended. We showed lately, that HES is a nephrotoxic agent and starch even reduced the kidney function in healthy animals, which was only seen

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in extended kidney diagnostic and histology [4–6]. As another new aspect, we could show that HES might protect blood–brain barrier (BBB) [7]. The detailed mechanism remains unclear. Furthermore, it seems that the risk of HES induced acute kidney injury (AKI) decreased, if HES is used for neurotrauma like stroke or subarachnoidal hemorrhage [8].

The so called Frank Starlings equation (FSE) is the theoretical background for the usage of colloid solutions to maintain hemodynamic stability. FSE implied that the driving force to reabsorb interstitial water back to the blood vessel, is the colloid osmotic pressure, mainly induced by albumin. Both the FSE, as well as the theory for the usage of colloids, are based upon a) a constant pressure in microcirculation and b) sealed microvessels (for macromolecules). However, this does not reflect the situation in critical ill patients (capillary leakage induced by e.g. sepsis) or perioperative setting (rapid vasoconstriction e.g. hemorrhage). Therefore, FSE was revisited by Woodcock et al. and others [9], and FSE theory was extended to reflect clinical settings (e.g. glycocalyx) [9]. Furthermore, Zhang et al. showed, that pediatric patients under the age of six showed no increase in colloid osmotic pressure after HES infusion [10]. Consequently, the question arose: Is there a need for an aged-related, extended Frank Starling Equation?

We conducted a single center, retrospective study to compare HES 130/0.4 with 5% human albumin for volume substitution in children under the age of five with at least 10% blood loss during neurosurgery, to bring more data to the topic synthetical colloids for neurosurgery in children.

## Main text

### Subjects and methods

This study was approved by the institutional review board of the Clinical Ethics Committee of the University of Würzburg, Germany, which waived the requirement for written informed consent because of the retrospective, observational nature of the study. This study included all children (< 5 years of age;  $n = 913$ ) from 2000 to 2007, who were admitted to the Department of Neurosurgery for neurosurgery. This included craniosynostosis—single suture and syndromic multisuture, crouzon synostosis, tumor (recurrence) with/-out hydrocephalus, tethered spinal cord, cerebral hemangioma, polytrauma with traumatic brain injury. In clinical routine, patients with > 10% of the estimated blood volume (eBV) received infusion of colloids either with HES or HA depending on the respective standard operating procedure for volume- and hemotherapy of the years 2000–2007. Patients with blood loss < 10% eBV were excluded. The eBV was calculated as 75 ml/kg body weight (BW). Patients were assigned to the

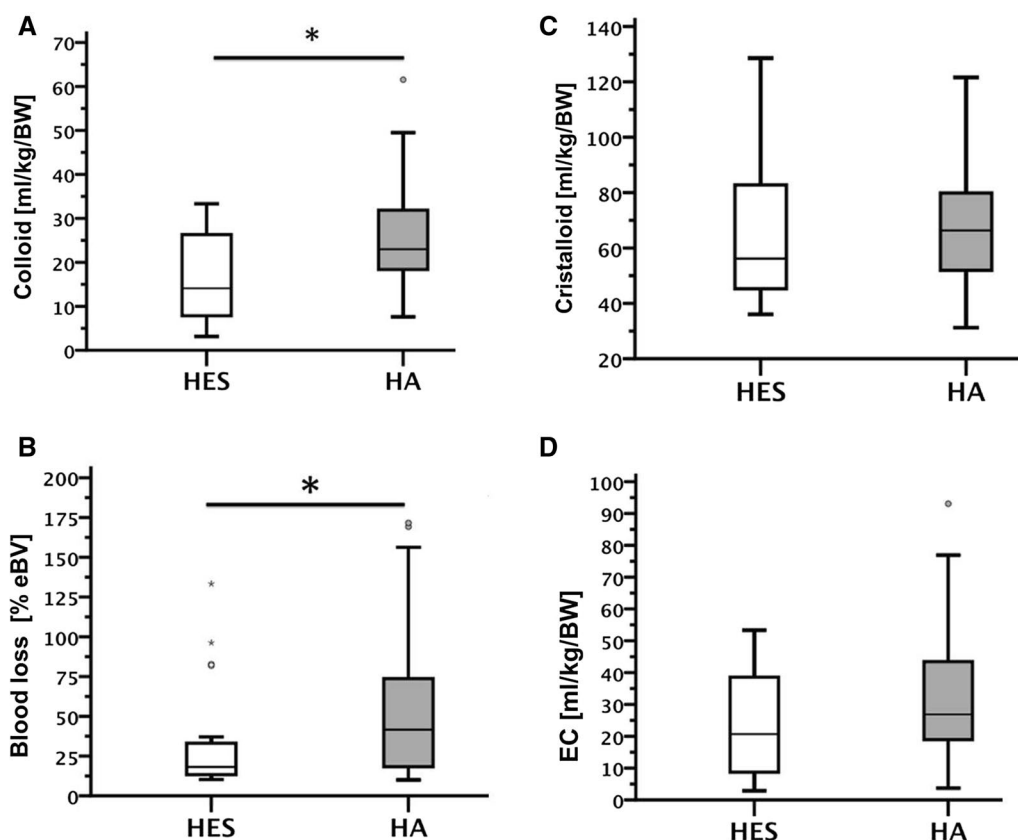
HES group ((HES); 6% HES 130/0.4; Fresenius Kabi, Bad Homburg, Germany) or to the 5% human albumin group (HA), when only HES or HA was infused during surgery and ICU (Fig. S1). The aim was the investigation of sole effects of HES or HA, therefore we excluded patients ( $n = 39$ ) who received HA and HES together.  $N = 22$  patients were excluded due to incomplete data,  $n = 2$  for other reasons and  $n = 764$  of blood loss < 10% eBV. Finally, 86 children were analyzed. Perioperative blood product transfusion in addition to fluid administration was performed according to the perioperative transfusion protocol of our institution (hemoglobin < 80 g/L and signs of anemia, acute blood loss > 15% of eBV or signs of hypovolaemia, instead of infusion therapy). Primary outcome was defined as total amount of colloids and secondary outcome parameters were length of ICU and hospital stay, ventilation time, coagulation and kidney parameter, blood loss.

### Statistical analysis

We compared HES with HA. Data derived from continuous variables are presented as medians and interquartile ranges (IQRs) or means  $\pm$  SD, and data derived from, categorical variables are presented as numbers and percentages. The normal distribution of the residuals was checked to assess the validity of the analysis. Preoperative and postoperative measurements were compared using Student's paired-t or the Mann–Whitney U test. Kruskal–Wallis test was used for data with an abnormal distribution of variance. The statistical significance of differences between the two groups a p-value of  $\leq 0.05$  was considered to be statistically significant in all comparisons. Multivariable analysis was not performed due to small sample sizes. Post hoc analysis was not done because it may not provide beneficial additional information. Calculations were performed using SPSS 26.0, IBM.

### Results

From 913 eligible patients, 86 fulfilled inclusion criteria with a documented blood loss > 10% of the eBV (75 ml/kgBW). HA infusion volumes were significantly higher than HES ( $25.7 \pm 11.3$  vs.  $16.4 \pm 9.2$  ml/kgBW, mean  $\pm$  SD,  $p = 0.001$ ). The gender distribution, weight and surgery duration did not differ between groups (Table S1). The cumulative amount of crystalloids were not different between the groups (HES  $66.7 \pm 27.5$  vs. HA  $68.1 \pm 21.9$  ml/kgBW, mean  $\pm$  SD,  $p = 0.967$ , Fig. 1). HA substituted patients had significantly more absolute blood loss ( $41.1 \pm 33.7$  vs.  $27.0 \pm 31.2$  ml/kgBW,  $p = 0.02$ ) and relative blood loss ( $54.8 \pm 45.0\%$  vs.  $30.5 \pm 30.0\%$  eBV,  $p = 0.04$ ) compared to HES. There was a trend toward the length of ICU stay and ventilation time, shorter in HA group and longer



**Fig. 1** Volume exchange (perioperative data): **A** Cumulative amount of HES or HA (ml/kg/BW). HA was significantly more infused than HES. **C** and **D** No differences were detected of crystalloid infusion and erythrocyte concentrates (EC) (ml/KG/BW). Blood loss in % of estimated blood volume. **B** HA group showed significantly more blood loss compared to HES. HES (6% HES 130/0.4), HA (Human albumin 5%), BW (body weight), eBV (estimated blood volume). \* $P < 0.05$ , compared between HES and HA, median  $\pm$  IQR

when tumor surgery alone was analyzed. ICU stay HES ( $40.23 \pm 25.14$ ) vs. HA ( $31.6 \pm 24.25$  [h],  $p = 0.131$ ), tumor surgery alone HES ( $54.15 \pm 26.34$ ) vs. HA ( $38.53 \pm 26.26$  [h],  $p = 0.066$ ), respectively). ICU ventilation time HES ( $21.27 \pm 16.0$ ) vs. HA ( $15.61 \pm 11.71$  [h]  $p = 0.067$ ), tumor surgery alone HES ( $29.6 \pm 16.8$  vs. HA ( $21.3 \pm 14.0$  [h])  $p = 0.127$ ).

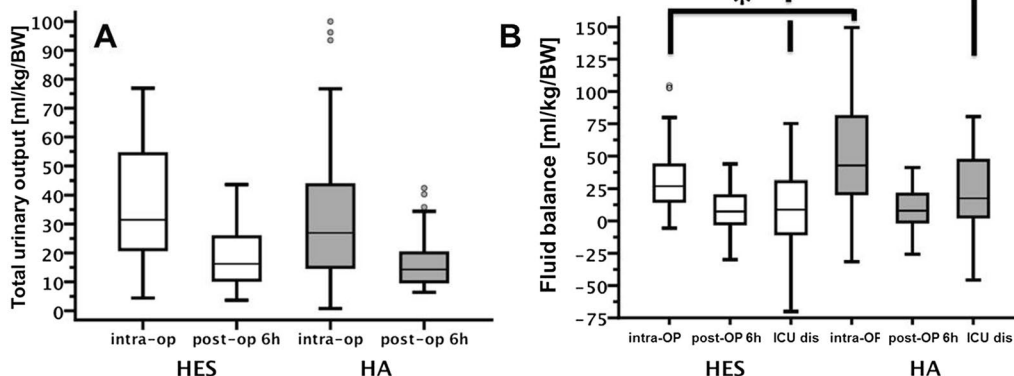
Application of erythrocyte concentrate did not differ between groups ( $31.9 \pm 19.9$  vs.  $24.0 \pm 18.1$  ml/kgBW,  $p = 0.179$ ). HA infusion volumes were significantly higher than HES infusion volumes ( $25.7 \pm 11.3$  vs.  $16.4 \pm 9.2$  ml/kgBW,  $p = 0.001$ ). Urinary output during surgery and within the first 6 h of ICU stay did not differ ( $p = 0.675$  and  $p = 0.385$ ), whereas fluid balance was significantly increased after surgery and after ICU stay in HA group ( $p = 0.03$  and  $p = 0.041$ ) (Fig. 2). Also no differences were detected between HA and HES regarding urea and creatinine ( $p = 0.807$  and  $p = 0.855$ ). Infusion of fresh frozen plasma was not different between groups ( $24.6 \pm 12.0$  vs.  $35.8 \pm 17.2$  ml/kgBW  $p = 0.234$ ), but aPTT was significantly increased in HA ( $p = 0.006$ ), and  $Ca^{2+}$  levels

decreased in HES group ( $p = 0.001$ ). Serum protein level were significantly increased in HA group when compared to HES ( $p = 0.001$ ) (Table 1).

## Discussion

To our knowledge, the present survey is the study with the most patients comparing HES and human albumin in children with neurosurgery procedures. Our main results show, that children undergoing neurosurgery with major blood loss received significantly more HA compared to HES. HA group had a higher rate of positive fluid balance and decreased coagulation parameters, whereas serum calcium and protein were significantly lower in the HES group.

Clinical trials regarding the use of synthetical colloids for infants are rare. The drawn conclusion, that HES is a safe alternative in the usage in infants, can only be stated by results of adequately powered clinical trials, which are missing. HES could be detected in liver, kidney, skin and immune cells. This may also have beneficial effects, e.g. for the graft kidney [11], despite the knowledge of HES



**Fig. 2** Fluid balance. **A** There were no differences between the groups regarding cumulative urine output (intraoperative and within the first 6 h of ICU). **B** There was a significant positive fluidbalance at the time-point end of surgery (intra-OP) and at discharge from ICU. \*p < 0.05 compared between HES and HA

**Table 1** Hematological data

		HES		HA	
		Baseline	ICU	Baseline	ICU
Blood count					
hb	[mmol/l]	7.64 ± 1.2*	6.64 ± 0.19	7.33 ± 0.06	6.40 ± 1.2
hct	[%]	35.7 ± 0.7	32.1 ± 0.8	36.7 ± 0.4	32.3 ± 0.6
Leucocyte	[10 <sup>3</sup> /μl]	9.6 ± 0.5	8.8 ± 0.5	10.6 ± 0.4	8.7 ± 0.4
Platlet	[10 <sup>3</sup> /μl]	379 ± 22	256 ± 14	401 ± 18	228 ± 11
Coagulation					
PT	[%]	99 ± 1	81 ± 2	97 ± 1	80 ± 2
aPTT	[sec]	34.4 ± 1.2	35.5 ± 1.2*	35.1 ± 0.8	41.2 ± 1.4
Fibrinogen	[mg/dl]	251.1 ± 13.8	189.5 ± 10.6*	262.2 ± 9.7	149.4 ± 6.8
Electrolyte					
Sodium	[mmol/l]	138 ± 1	140 ± 1	138 ± 0	140 ± 0
Potassium	[mmol/l]	4.6 ± 0.1	3.9 ± 0.1	4.6 ± 0.1	3.8 ± 0.1
Calcium	[mmol/l]	2.45 ± 0.04*	1.78 ± 0.89*	2.5 ± 0.2	2.29 ± 0.04
Kidney					
Creatinine	[mg/dl]	0.30 ± 0.02	0.3 ± 0.02	0.31 ± 0.01	0.32 ± 0.01
Urea	[mg/dl]	22.6 ± 2.1	17.9 ± 1.4	23.0 ± 1.9	19.8 ± 2.3
Liver					
ALT	[U/l]	19 ± 1.8	13 ± 1.0*	16 ± 1.0	10 ± 0.6
GGT	[U/l]	16.3 ± 4.2	9.8 ± 1.3	8.5 ± 0.7	9 ± 1.8
Total serum protein	[g/dl]	6.8 ± 0.1	4.5 ± 0.1*	6.6 ± 0.1	5.2 ± 0.1
BG	[mg/dl]	n.a	115 ± 4.8	n.a	110 ± 3.6

Data are mean ± SEM. HES (6% HES 130/0.4), HA (Human albumin 5%) \*p < 0.05 compared between HES and HA. *Hb* hemoglobin, *hct* hematocrit, *prothrombin time*, *PT*, *ALT* alanine transaminase, *GGT* gamma-glutamyl transferase, *BG* blood glucose

induced AKI. However, the impact of HES on a not fully developed (infant) kidney is not known. To our knowledge, there are no human data available to answer this question. Our presented results showed no differences in standard kidney parameter and urinary output. But

in regard to our previous data, this must be examined carefully, since HES induced AKI may only be detected in enlarged kidney diagnostic, such as biopsy and inulin clearance [4]. HA infants showed a positive fluid balance

at the end of surgery and ICU stay. We cannot exclude that infused HA had a long lasting extravasal volume effect due to perioperative capillary leakage. Despite the positive fluid balance, the HA group tended to have reduced ventilation time and length of hospital stay, especially in tumor surgery. It was published that HES does not cross the BBB and it is not found in cerebral tissue [8, 12]. However, HES accumulation in destroyed cerebral regions, induced by trauma or surgery, cannot be excluded. Incorporation of HES, in e.g. hypoxic neurons, may have a beneficial effect for survival due to the ability of HES to inhibit formation of reactive oxygen species [8], whereas albumin can be deleterious for astrocyte or neuronal functions by modulating potassium ion and glutamate concentrations, which is driving epileptogenesis [13–15]. HA was associated with higher mortality rates in traumatic brain injury, in contrary HES showed better survival rates (sequential network meta-analyses of 26,351 patients [16]). In this context, the usage of HA for neurosurgery might also be discussed. Due to high cost and limited availability of HA, the need for alternative substances, like HES, remains high. We chose the time-frame for the retrospective study because at that time a maximum dosage of 50 ml/kgBW HES application was allowed. Today's recommendation by Werner et al. suggests a maximal dosage of 18.8 ml/kgBW 6% HES 130/0.4 in order to prevent the development of HES induced AKI [17]. As expected, in our trial HES was infused up to 33 ml/kgBW, which can result in a high impact on the infants. HA has no recommended maximum dosage, and thus HA was given up to an amount of 62 ml/kgBW in this survey. There were no changes in ventilation time, nor days to discharge after surgery, when the dosage of >30 ml/kg/BW HA was infused. This raises the questions, whether we need to generally revisit the perioperative usage of HA and, moreover, if we need a maximum threshold adjusted to age. Unexpectedly, serum  $\text{Ca}^{2+}$  was significantly reduced in HES patients after surgery. This phenomenon is known, but occurs rarely and is hardly described [18, 19]. The serum  $\text{Ca}^{2+}$  level is in an equilibrium with  $\text{Ca}^{2+}$  level in the cerebrum. A decreased level of  $\text{Ca}^{2+}$  in neurons can be protective [8]. Therefore, reduced  $\text{Ca}^{2+}$  might be an advantage for the cellular survival in the penumbra, but is a disadvantage for the coagulation system since decreased  $\text{Ca}^{2+}$  levels reduce its efficiency. HES impaired coagulation system in different ways and reduced clot formation in adults as well as in children [20]. Our results showed normal parameters in the HES group, whereas HA application decreased fibrinogen, increased PTT and blood loss. HA can inhibit platelet aggregation or act via heparin-like effects via antithrombin III [21–23]. If HA was used for hemodilution in vitro, it showed hypocoagulation over 25% [24].

## Conclusion

Prospective randomized controlled trials are required to provide evidence-based knowledge on perioperative goal-directed infusion therapy in small children undergoing surgery with major blood loss. Children receiving HA infusion showed decreased coagulation parameters, increased blood loss, increased colloid volumes and positive fluid balance, compared to children receiving HES infusion. Renal function revealed no differences between groups. Our data do not allow recommendations whether to infuse HES or HA during pediatric neurosurgery.

## Limitations

First, despite of 913 patients under the age of five years only 86 could be included with blood loss >10% eBV and infusion of either HA or HES. This small number of patients, in a single center retrospective observation study, weakens the value of the results. As far as we know, we analysed the most extensive data about volume substitution in pediatric patients receiving neurosurgery procedures. Second, 50% of the performed surgery was tumor surgery, which reduces the overall comparability. Though, the ratio within the two groups (tumor -/ other surgery) was similar [HES 50/50, HA 46/54 (%).] Third, the guidelines for perioperative intravenous fluid therapy for children is permanently changing [25]. However, the results of the survey remain valid, since both substances are still utilized for pediatric patients.

## Abbreviations

AKI: Acute kidney injury; BW: Body weight; CL: Crystalloid; COL: Colloid; eBV: Estimated blood volume; FSE: Frank Starling equation; GDFT: Goal directed fluid therapy; HA: Human albumin; HES: Hydroxyethylstarch; ICU: Intensive care unit.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13104-021-05836-w>.

**Additional file 1: Figure S1.** Study population (CONSORT statement). UKW (University hospital of Würzburg), HES (hydroxyethylstarch), HA (human albumin).

**Additional file 2: Table S1.** Population and clinical characteristics (mean ± SD).

**Additional file 3.** CONSORT 2010 checklist of information to include when reporting a randomised trial.

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Not applicable.

## Authors' contributions

MAS concept and design, data acquisition, analysis and interpretation of data, drafting and editing of the manuscript; JP: data acquisition, analysis and interpretation of data, drafting and editing of the manuscript drafting and editing

of the manuscript; MS: interpretation of data, drafting and editing of the manuscript; JB: interpretation of data, drafting and editing of the manuscript; WN interpretation of data, drafting and editing of the manuscript; CW analysis and interpretation of data, drafting and editing of the manuscript; All authors read and approved the final manuscript.

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#### Availability of data and materials

Request to: martin.schick@uniklinik-freiburg.de.

#### Declarations

#### Ethics approval and consent to participate

This study was approved by the institutional review board of the Clinical Ethics Committee of the University of Würzburg, Germany, which waived the requirement for written informed consent because of the retrospective, observational nature of the study.

#### Consent for publication

Not applicable.

#### Competing interests

Author reports no conflict of interest associated with this manuscript.

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#### References

- Lehr AR, Rached-d'Astous S, Parker M, McIntyre L, Sampson M, Hamid J, et al. Impact of balanced versus unbalanced fluid resuscitation on clinical outcomes in critically ill children: protocol for a systematic review and meta-analysis. *Syst Rev*. 2019;8(1):195.
- Shin CH, Long DR, McLean D, Grabitz SD, Ladha K, Timm FP, et al. Effects of intraoperative fluid management on postoperative outcomes: a hospital registry study. *Ann Surg*. 2018;267(6):1084–92.
- Thy M, Montmayeur J, Julien-Marsollier F, Michelet D, Brasher C, Dahmani S, et al. Safety and efficacy of peri-operative administration of hydroxyethyl starch in children undergoing surgery: a systematic review and meta-analysis. *Eur J Anaesthesiol*. 2018;35(7):484–95.
- Schick MA, Baar W, Bruno RR, Wollborn J, Held C, Schneider R, et al. Balanced hydroxyethylstarch (HES 130/0.4) impairs kidney function in-vivo without inflammation. *PLoS ONE*. 2015;10(9):e0137247.
- Schick MA, Isbary TJ, Schlegel N, Brugger J, Waschke J, Muellenbach R, et al. The impact of crystalloid and colloid infusion on the kidney in rodent sepsis. *Intensive Care Med*. 2010;36(3):541–8.
- Bruno RR, Neuhaus W, Roewer N, Wunder C, Schick MA. Molecular size and origin do not influence the harmful side effects of hydroxyethyl starch on human proximal tubule cells (HK-2) in vitro. *Anesth Analg*. 2014;119(3):570–7.
- Gerhartl A, Hahn K, Neuhoff A, Friedl HP, Forster CY, Wunder C, et al. Hydroxyethylstarch (130/0.4) tightens the blood-brain barrier in vitro. *Brain Res*. 2020;1727:146560.
- Schick MA, Burek M, Forster CY, Nagai M, Wunder C, Neuhaus W. Hydroxyethylstarch revisited for acute brain injury treatment. *Neural Regen Res*. 2021;16(7):1372–6.
- Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth*. 2012;108(3):384–94.
- Zhang JZ, Liu JS, Zhang SH, Huang SY, Zhang JJ, Zhou J, et al. Distinctive effect of 6% hydroxyethyl starch 130/0.4 (Volumen) infusion on pediatric patients with congenital heart disease. *Eur Rev Med Pharmacol Sci*. 2017;21(6):1384–96.
- Vuiblet V, Fere M, Bankole E, Wynckel A, Gobinet C, Birembaut P, et al. Raman-based detection of hydroxyethyl starch in kidney allograft biopsies as a potential marker of allograft quality in kidney transplant recipients. *Sci Rep*. 2016;6:33045.
- Somova LM, Moldavanov MA, Plekhova NG, Shumatov VB. Morphological validation of hydroxyethylstarch use during the acute period of severe brain injury. *Bull Exp Biol Med*. 2013;155(3):403–7.
- Taberner A, Granda B, Medina A, Sanchez-Abarca LI, Lavado E, Medina JM. Albumin promotes neuronal survival by increasing the synthesis and release of glutamate. *J Neurochem*. 2002;81(4):881–91.
- David Y, Cacheaux LP, Ivens S, Lapilover E, Heinemann U, Kaufer D, et al. Astrocytic dysfunction in epileptogenesis: consequence of altered potassium and glutamate homeostasis? *J Neurosci*. 2009;29(34):10588–99.
- Lapilover EG, Lippmann K, Salar S, Maslarova A, Dreier JP, Heinemann U, et al. Peri-infarct blood-brain barrier dysfunction facilitates induction of spreading depolarization associated with epileptiform discharges. *Neurobiol Dis*. 2012;48(3):495–506.
- Tseng CH, Chen TT, Wu MY, Chan MC, Shih MC, Tu YK. Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses. *Crit Care*. 2020;24(1):693.
- Werner J, Hunsicker O, Schneider A, Stein H, von Heymann C, Freitag A, et al. Balanced 10% hydroxyethyl starch compared with balanced 6% hydroxyethyl starch and balanced crystalloid using a goal-directed hemodynamic algorithm in pancreatic surgery: a randomized clinical trial. *Medicine (Baltimore)*. 2018;97(17):e0579.
- Jamnicki M, Bombeli T, Seifert B, Zollinger A, Camenzind V, Pasch T, et al. Low- and medium-molecular-weight hydroxyethyl starches: comparison of their effect on blood coagulation. *Anesthesiology*. 2000;93(5):1231–7.
- Kwak HJ, Lim OK, Baik JM, Jo YY. Acid/base alterations during major abdominal surgery: 6% hydroxyethyl starch infusion versus 5% albumin. *Korean J Anesthesiol*. 2018;71(6):459–66.
- Peng Y, Du J, Zhao X, Shi X, Wang Y. Effects of colloid pre-loading on thromboelastography during elective intracranial tumor surgery in pediatric patients: hydroxyethyl starch 130/0.4 versus 5% human albumin. *BMC Anesthesiol*. 2017;17(1):62.
- Rao AK, Koike K, Day HJ, Smith JB, Holmsen H. Bleeding disorder associated with albumin-dependent partial deficiency in platelet thromboxane production. Effect of albumin on arachidonate metabolism in platelets. *Am J Clin Pathol*. 1985;83(6):687–96.
- Jorgensen KA, Stoffersen E. On the inhibitory effect of albumin on platelet aggregation. *Thromb Res*. 1980;17(1–2):13–8.
- Joergensen KA, Stoffersen E. Heparin like activity of albumin. *Thromb Res*. 1979;16(3–4):569–74.
- Tobias MD, Wambold D, Pilla MA, Greer F. Differential effects of serial hemodilution with hydroxyethyl starch, albumin, and 0.9% saline on whole blood coagulation. *J Clin Anesth*. 1998;10(5):366–71.
- Sumpelmann R, Becke K, Brenner S, Breschan C, Eich C, Hohne C, et al. Perioperative intravenous fluid therapy in children: guidelines from the Association of the Scientific Medical Societies in Germany. *Paediatr Anaesth*. 2017;27(1):10–8.

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