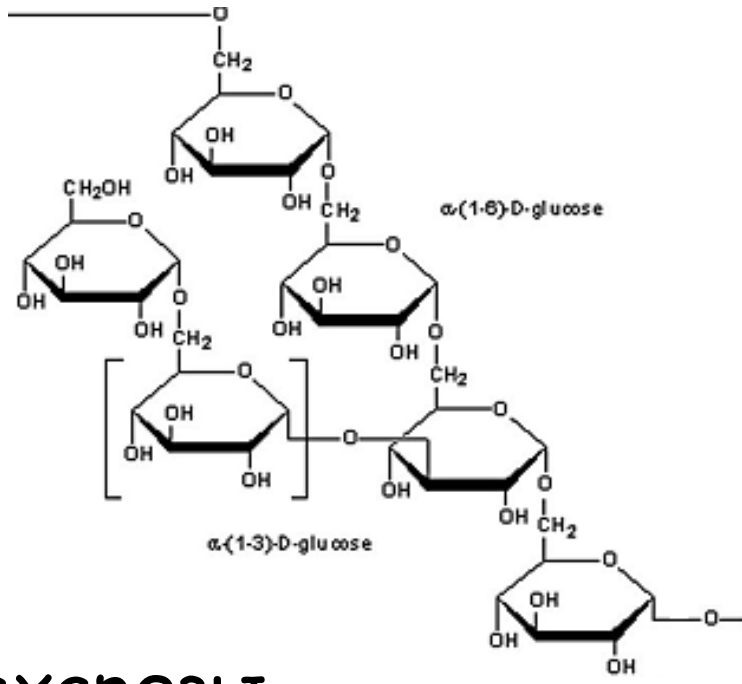
Изменение подходов к использованию коллоидов

В.А. Мазурок

СЗФМИЦ им. В.А. Алмазова
Санкт-Петербург

Декстраны



- Гликополисахарид
- Энзиматический синтез из сахарозы
  - Leuconostoc mesenteroides (dextranicum)
- 1944 г. – первый коммерческий dextran 75
  - Groönwall A & Ingelman B. Acta Physiologica Scandinavica 1944; 7: 97–107.
- 1952 г., сентябрь - разрешен FDA

Декстраны

- 1952 г. – Ленинградский НИИ гематологии и переливания крови: синкол
  - Кочетыгов Н.И. Кровезаменители при кровопотере и шоке. "Медицина", Л.,1984
- 1954 г. – Центральный НИИ гематологии и переливания крови: полиглюкин

Декстраны

- 1 г декстрана связывает 20-25 мл воды
- 1 г альбумина - 17 мл
- Волемический эффект 10% декстрана-40 ≈200%

- Малышев В.Д. Интенсивная терапия. М.,1997.
- Singl S.,Schaeffer R.C.,Valdes S. Crit. Care Med. 1983. V.33 p.585-590.

Декстраны

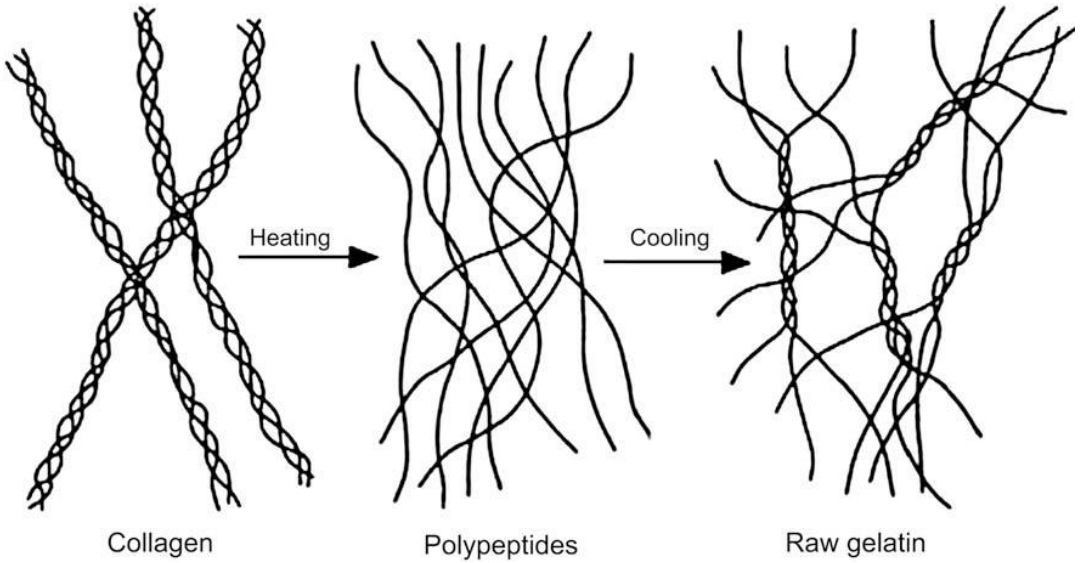
- Дешевы, хранятся при комнатной t (до 10 лет)
  - Aktories K. General and specific pharmacology and toxicology. 9th edn. Munich: Elsevier, Urban & Fischer, 2006.
- Эффективная тромбопрофилактика
  - Koekenberg LJ. Bulletin de la Socie.te. Internation de Chirurgie 1962; 21: 501–512.
- Сравнимая с нефракционированным гепарином
  - Gruber UF. The British Journal of Surgery 1982; 69(Suppl.): S54–S58.
  - Gruber UF, Saldeen T, Brokop T et al. British Medical Journal 1980; 280: 69–72.
  - Hohl MK, Luscher KP, Tichy J et al. Obstetrics and Gynecology 1980; 55: 497–500.

Декстраны?

- Не вступили на путь эволюции.
- Практически забыты.

Желатины

- Из коллагена крупного рогатого скота
  - Денатурация и гидролизация
  - Полипептидные сшитые фракции



C. Ertmer et al. / Best Practice & Research Clinical Anaesthesiology 23 (2009) 193–212

Желатины

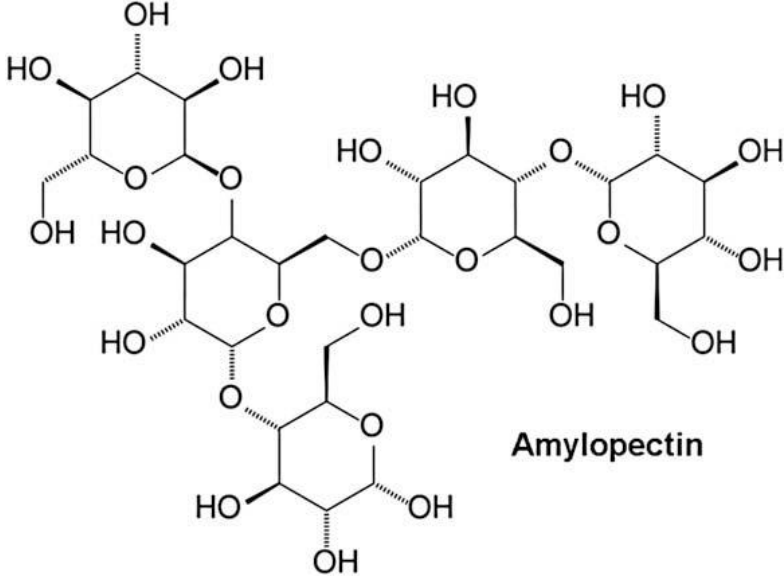
- Осмотический диурез (30–45 kDa)
  - ~ 50% экскретируется с мочой во время или вскоре после инфузии
  - Необходимость добавления кристаллоидов

Желатины

- Гистаминолибераторы
  - Тяжелые реакции – у 0.05–0.1% пациентов
  - С 1978 г. в США не используются
    - Boldt J. Can. J. Anaesth. – 2004. – V. 51, № 5. – P. 500–513.

- Теоретический риск передачи спонгиформной энцефалопатии (прион)
  - Ragaller M.J.R., Theilen H., Koch T. J. Am. Soc. Nephrol. – 2001. – V. 12, Suppl. 17. – P. S33–39.

ГЭК



- Амилопектин – высоко разветвленный полимер глюкозы
  - Сходство с натуральным коллоидом
- Низкая вязкость, хотя и > альбумина

ГЭК

- 1934 г. – синтезированы для промышленных целей
- 1957 г. – экспериментальное использование в качестве плазмозаменителя
  - Wiedersheim M. Archives Internationales de Pharmacodynamie et de Therapie 1957; 111: 353-361.
- 1964–1975 гг. – широкое применение во время войны во Вьетнаме

Еще совсем недавно…

Тетра-ГЭК –

все ближе к идеалу

ГЭК 130/0.4

- **Наименее выраженное действие**
  - Буланов А.Ю., Городецкий В.М. и др. Анестезиол. и реаниматол. 2004; 2: 25-9.
  - Baron J. F. И Tranfus. Aiternat. Transfus. Med. - 2000. -Vol.2. - №2.- P. 13-21.
  - Haisch G., Botdt J. et al. // J. Cardiothorac. Vas. Anesth. - 2001. (15): 316-321.
  - Katsuda K., Maeno H. // Thromb. Res. - 1980. - Vol. 19. -P. 655-662.
- **Только дилюция в отличие от др. ГЭК**
  - Asskali F., Lehmann G., Forster H. // Anasthesiol. Intensivmed. Notfallmed. Schmcrzther. - 2002. - Bd. 37. - S. 258-266.
  - Baron J. F. И Tranfus. Aiternat. Transfus. Med. - 2000. -Vol.2. - №2.- P. 13-21.
  - Gailandat R.C.G., Siemens A. W. et al. // Can.J. Anaesth. – 2000 (47)12:1207-1215.
  - Haisch G., Botdt J. et al. // J. Cardiothorac. Vas Anesth. - 2001. (15): 316-321.
  - Entholzner EK et al. *Acta Anesthesiol Scand 2000; 44: 1116-21*

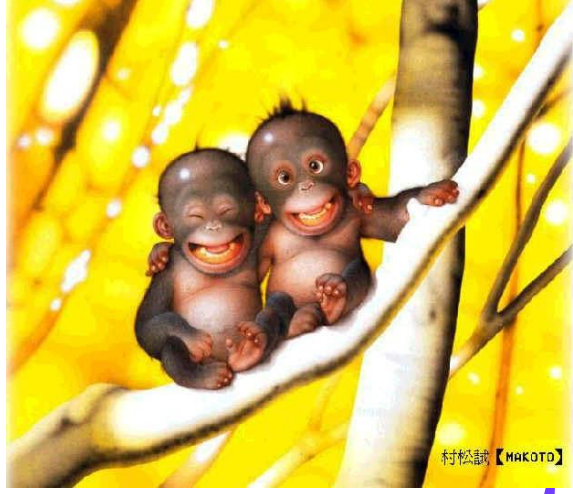
Тетра-ГЭК

- ***Влияние на гемостаз клинически незначимо***
  - de Jonge E., Levi M. // Crit. Care Med. – 2001. – V. 29, № 6. – P. 1261–1267.
  - Dieterich H. J., Haeberle H. A., Nohe B. In: Yearbook of intensive care and emergency medicine/ Vincent J.-J. (eds). – Berlin: Springer-Verlag. – 2004 - P. 714–721.
  - Imm A., Carlson R. W. // Crit. Care Clin. – 1993. – V. 9, № 2. – P. 313–333
  - Sander O, Reinhart K et al. Acta Anaesthesiologica Scand 2003; 47 1151-1158
- ***Препараты выбора***
  - С.Г. Решетников, А.В. Бабаянц, Д.Н. Проценко, Б.Р. Гельфанд. Инфузионная терапия в периоперационном периоде (обзор литературы) // Интенсивная терапия. - N1 - 2008 г.

Коллоиды при ОПЛ/РДСВ

- **Оценка безопасности остается актуальной**
  - Vincent J.-L. Crit Care. - 2000. - Vol. 4. - Suppl. 2. - P. SI-S2.

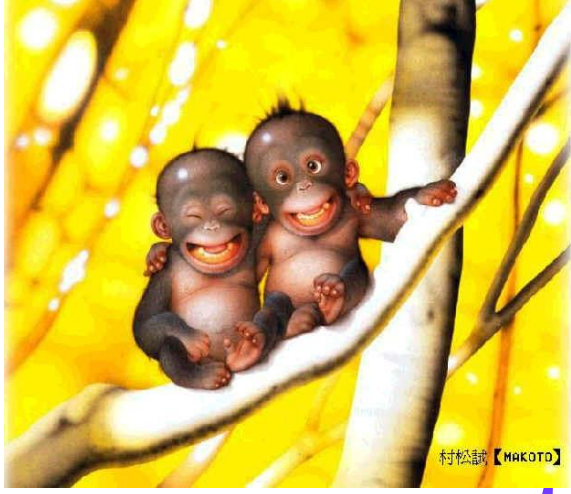
Коллоиды при ОПЛ/РДСВ



- ГЭК (эксперимент)
  - ↓ легочной сосудистой проницаемости
  - ↓ интерстициального отека

- Groeneveld J. Crit Care. - 2000. - Vol. 4. - Suppl. 2. -P. S16-S20.
- Tian J., Lin X., Guan R., Xu J.-G. Anesth. Analg. - 2004. - Vol. 98. - P. 768-774.
- Webb A.R., Tighe D., Moss R.F. et al. Crit. Care Med. -1991. - Vol. 19. - P. 409-416.
- Webb A.R., Moss R.F., Tighe D. et al. Intensive Care Med. - 1992. - Vol. 18. - P. 348-355.

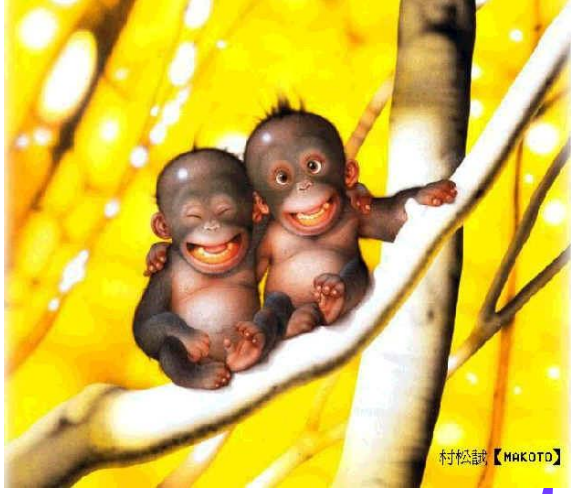
ГЭК – проницаемость капилляров



- РКИ (45 пац.): ГЭК 250/0,45 / желатин / альбумин
  - **ГЭК 250/0,45 ↓ проницаемость сосудов почек**
    - ↓ экскреция альбумина, ↓ степень поражения легких
  - **ГЭК 250/0,45 ↓ посттравматическую капиллярную утечку**
  - Максимальная почечная экскреция альбумина - группа желатина

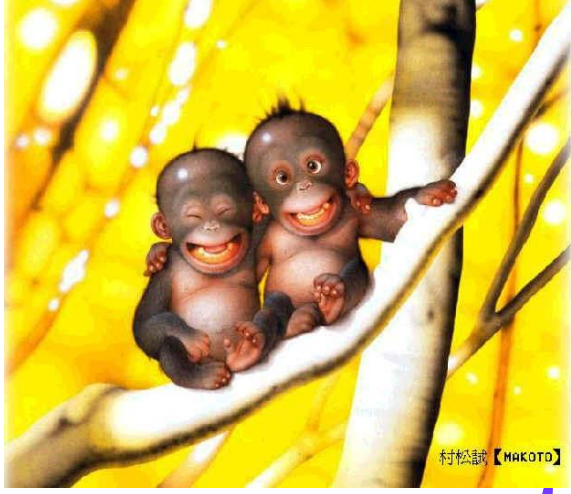
Allison K. P., Gosling P., Jones S. et al. J. Trauma. – 1999. – V. 47, № 6. – P. 1114–1121

ГЭК – проницаемость капилляров



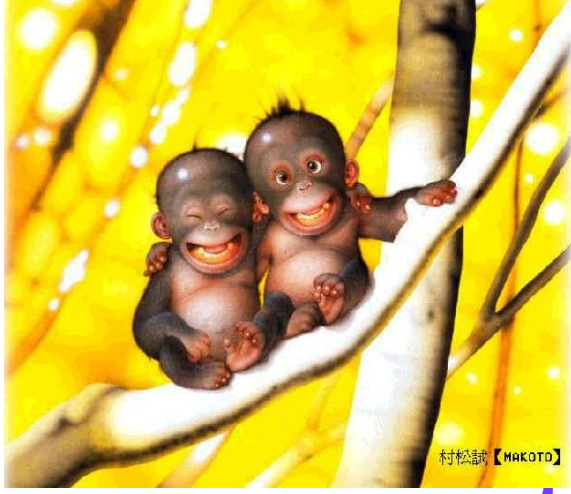
- **Препараты выбора при повреждении эндотелия и ↓ КОД плазмы**
  - Шифман Е. М., Тиканадзе А. Д. Инфузионная терапия периоперационного периода: что, кому и сколько? – Петрозаводск: ИНТЕЛТЕК, 2001

ГЭК – проницаемость капилляров



- ГЭК 130/0,4 - влияние на эндотелий (*мыши*)
  - ↓ постгипоксических явлений
  - **↓ капиллярной утечки и признаков СВР**
    - Dieterich HJ. J Trauma 2003; 54(suppL 5): S26-30
- РКИ: ГЭК 130/0,42/ГЭК 200/0,5 (*свиньи, септич. шок*)
  - **130/0,42 эффективнее ↓ проницаемость капилляров**
    - Marx G, Pedder S, Smith L et at. Shock 2004; 21: 336-41

ГЭК – проницаемость капилляров



- Ранняя инфузия ГЭК 130/0,4 (*крысы, сепсис*)
  - ↓↓ концентрации медиаторов воспаления
  - **↓ патологической проницаемости**
    - Feng X. Hu Y. Ding J. et al. Ann Clin Lab Sci 2007; 37: 49-56.

ГЭК – проницаемость капилляров

- Мета-анализ 12 РКИ (1062 пац.): сепсис
  - Оптимальный раствор неизвестен
  - Тенденция к ↑ летальности! (↓ вероятности выживания)
    - ↑ Летальности ($p < 0.001$) при > 22 мл/кг*день, чем при <дозах!
  - ↑ ОПН по сравнению с ГЭК + желатин

Не использовать при сепсисе!!

- Wiedermann CJ. BMC Emerg Med. 2008 Jan 24;8:1.

А разные синтетические коллоиды?

- Мета-анализ 63 РКИ: (травма, ожоги, хирургия)
  - 23 РКИ (7.754 пац.): альбумин и белковые фракции
  - 16 РКИ (637 пац.): ГЭК/кристаллоиды
  - 11 РКИ (506 пац.) : модиф. желатин/кристаллоиды
  - 9 РКИ (834 пац.): декстран/кристаллоиды
  - 8 РКИ (1283 пац.): декстран на гипер. кристалл./кристаллоиды
- **Коллоиды ≈ риск смерти**
  - **Дóроги + ≈выживаемость – аргументы?**
    - Perel P, Roberts I. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD000567

А разные синтетические коллоиды?

- Мета-анализ: **нет отличий в клинических исходах**
  - Bunn F, Trivedi D & Ashraf S. Cochrane Database of Systematic Reviews (Online) 2008; 1. CD001319.

www.ccmjournal.org February 2013 • Volume 41 • Number 2

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

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Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8];
Ivor S. D[illegible]y, MD[12];
Sean R. T[illegible]
Derek C. [illegible];
Gordon [illegible]
Jean-Lou[illegible]
Guideline[illegible]

Crit Care Med 2008 Vol. 36, No. 1

Special Article

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maurene Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee

Special Articles

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ТЕПЕРЬ ВСЕ ЯСНО!...

Что?

- Рекомендуем не применять HES при сепсисе/септическом шоке (1B).
  - VISEP, CRYSTMAS, 6S, CHEST. Кроме CRYSTAL

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012
R. Phillip Dellinger, Mitchell M. Levy, Andrew Rhodes, Djillali Annane et al.

Crit Care Med 2013

Что?

коллоиды или кристаллоиды?

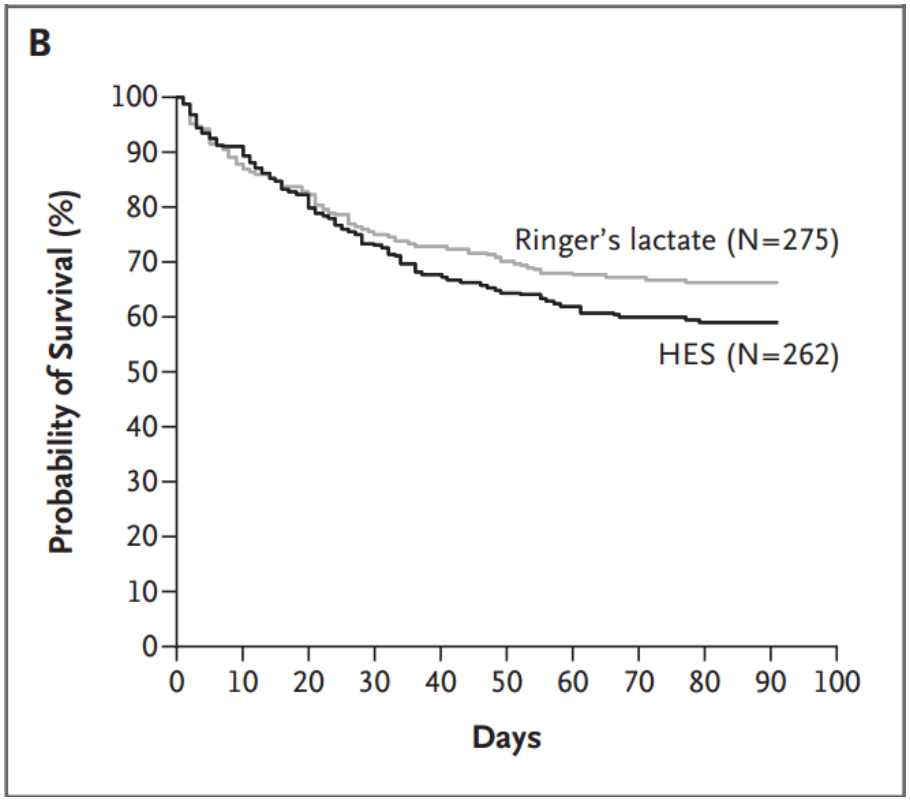
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2008;358:125-39.

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Visep: "HES kills patients!"



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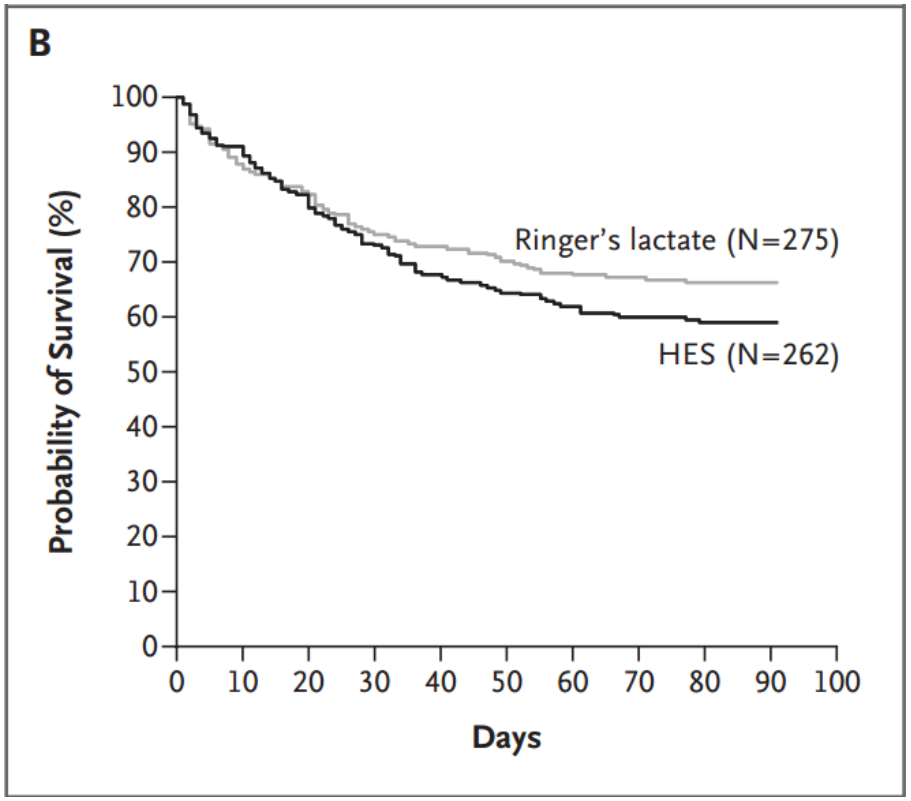

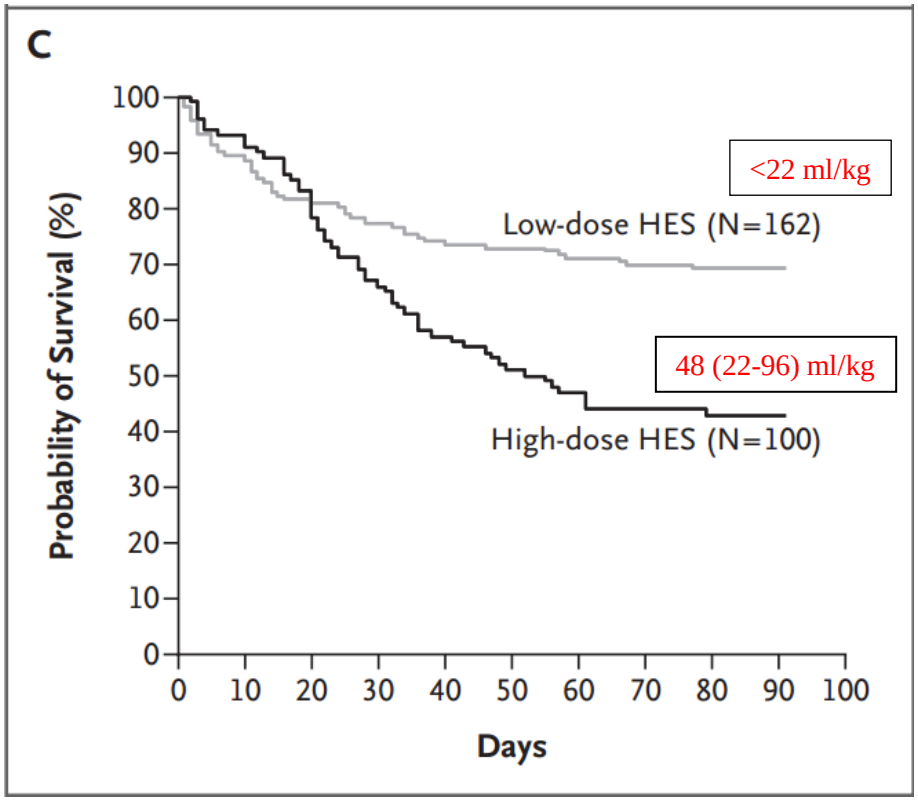

Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: A randomized, three-way crossover study in healthy volunteers

Dileep N. Lobo, DM, FRCS; Zeno Stanga, MD; Mark M. Aloysius, MRCS; Catherine Wicks, BMedSci, BM, BS; Quentin M. Nunes, MRCS; Katharine L. Ingram, FRCA; Lorenz Risch, MD, MPH; Simon P. Allison, MD, FRCP

Crit Care Med. 2010 58(2):1-7

10 добровольцев
1000 мл жидкости/60 мин

Коллоиды – да

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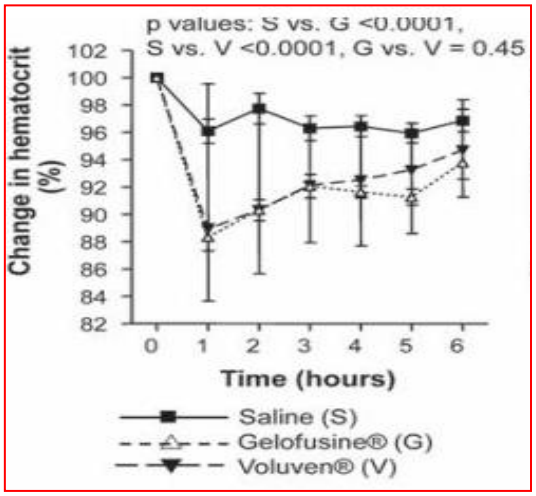

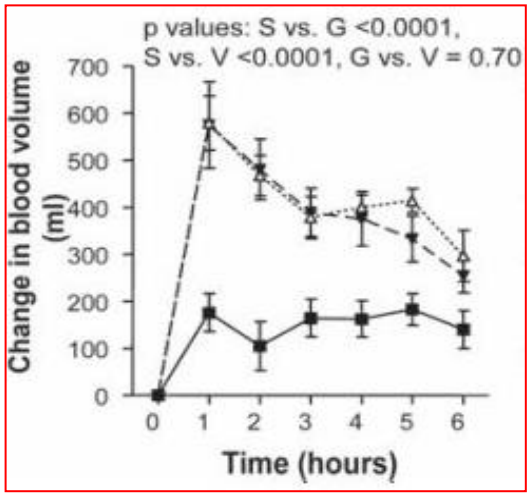

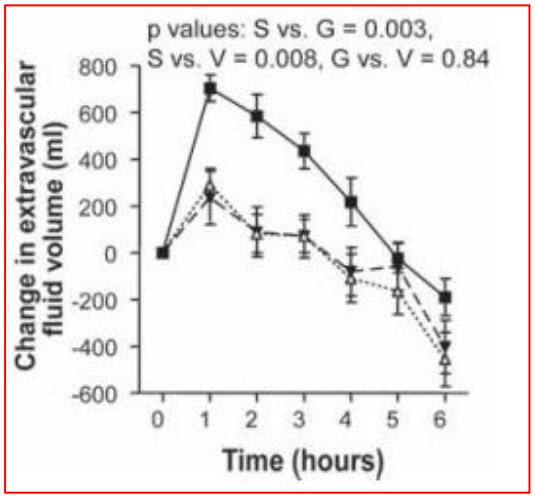

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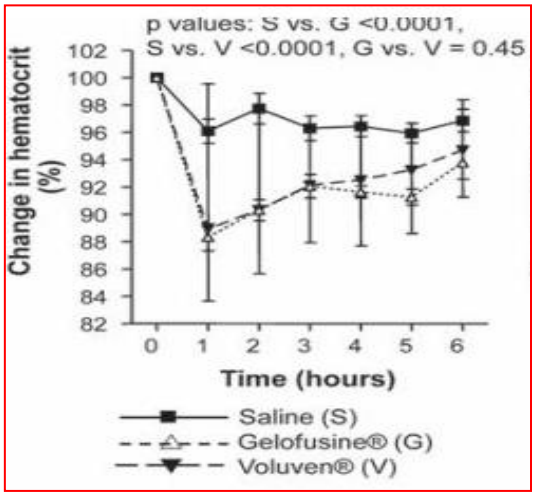
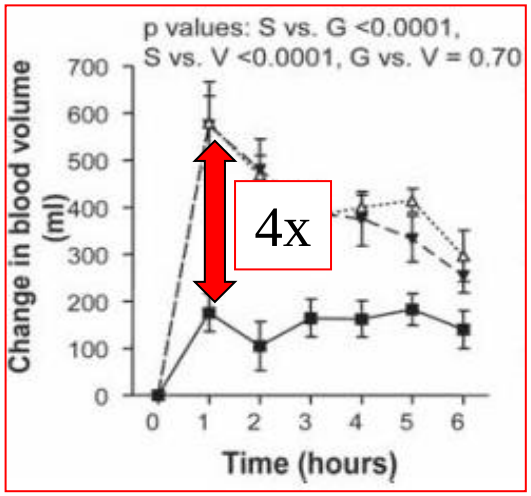
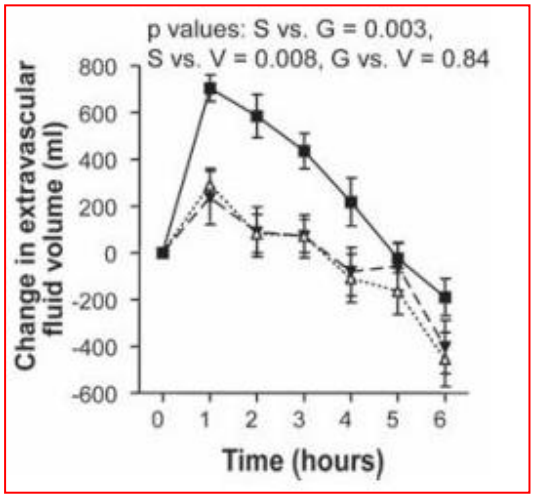






Коллоиды – да

Guidet et al. Critical Care 2012, 16:R94
http://ccforum.com/content/16/3/R94

CRITICAL CARE

CRYSTMAS 2012

RESEARCH Open Access

Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

Bertrand Guidet[1,2,3*], Olivier Martinet[4], Thierry Boulain[5], Francois Philippart[6,7], Jean François Poussel[8], Julien Maizel[9], Xavier Forceville[10], Marc Feissel[11], Michel Hasselmann[4], Alexandra Heininger[12] and Hugo Van Aken[13]

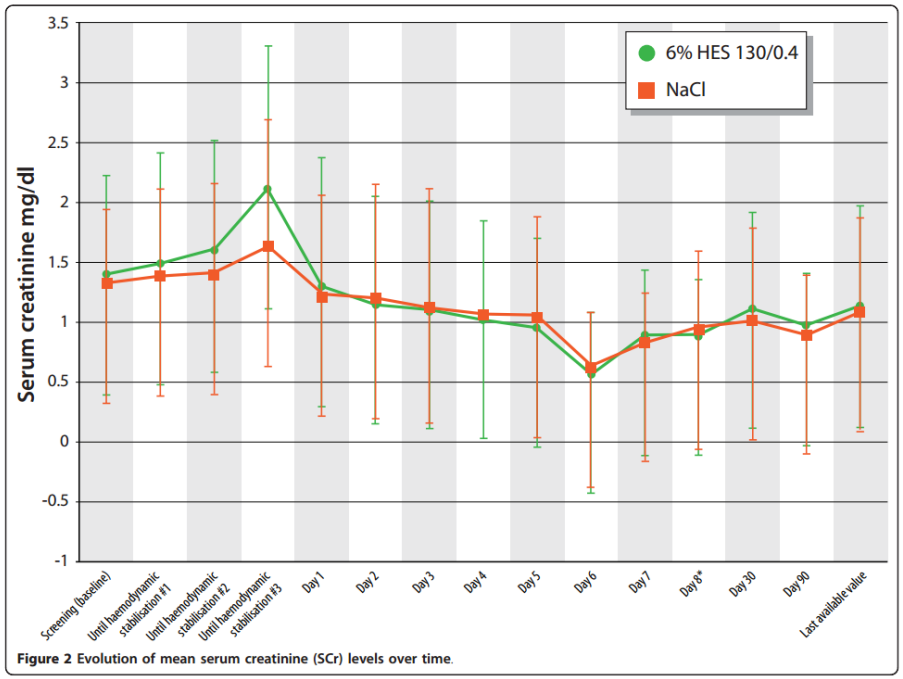


Figure 2 Evolution of mean serum creatinine (SCr) levels over time.

Количество жидкости для стабилизации гемодинамики?

Results: 174 out of 196 patients reached HDS (88 and 86 patients for HES and NaCl, respectively).

Conclusion: Significantly less volume was required to achieve HDS for HES vs. NaCl in the initial phase of fluid resuscitation in severe sepsis patients without any difference for adverse events in both groups.

Коллоиды – да

CRYSTMAS 2012
критика

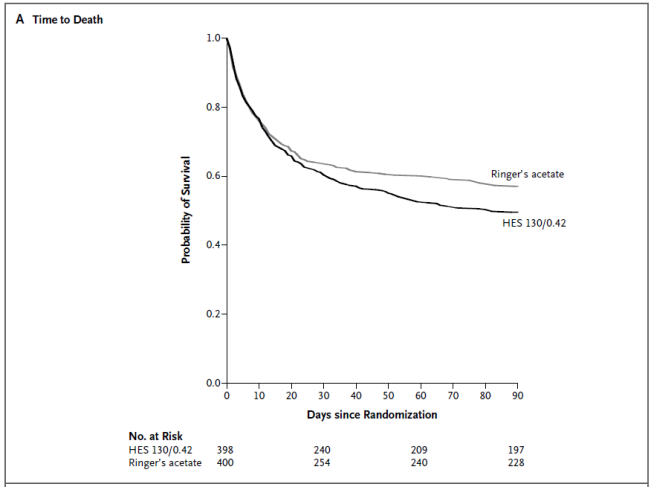
- **Нет данных о:**
  - *Параметрах гемодинамики или лактата* (**нужна ли инфузия?**)
  - *Общем объеме инфузии* (исследуемом + дополнительном)
- **Разнородность групп:**
  - …HES пациенты получали раньше и меньше калорий при энтеральном питании
- …выборка (n=196) мала для статистики о летальности
- **Не указан алгоритм оценки эффективности инфузии!**

Коллоиды – нет

ORIGINAL ARTICLE

N ENGL J MED 367;2 NEJM.ORG JULY 12, 2012

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis



6S-Trial

METHODS Of the 804 patients who underwent randomization, 798 were included. In this multicenter, parallel-group, blinded trial, we randomly assigned patients with severe sepsis to fluid resuscitation in the ICU with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate at a dose of up to 33 ml per kilogram of ideal body weight per day. The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) at 90 days after randomization.

CONCLUSIONS

Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, as compared with those receiving Ringer's acetate.

Коллоиды – нет?

6S-Trial критика

- **Кристаллоидная группа – не кристаллоидная!**
  - До 1 л. синтетических коллоидов разрешено до рандомизации
- HES группа - >на 1 дозу RBC
- **HES противопоказаны при ОПН** (инструкция):
  - Однако такие пациенты включены в обе группы
  - HES – лекарство! Соблюдать инструкцию!
- Дизайн: макс.суточная доза 33 ml/kg IBW
  - На деле, 44 ml/kg (24–75 ml/kg) в HES группе
    47 ml/kg (25–76 ml/kg) в кристалл. группе

~3000 ml (!)

Коллоиды – нет?

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~3000 ml (!)

6S-Trial критика

- Согласно SSC (2012), **минимум 25% пациентов** были **стабильны и не нуждались с инфузии.**
- У 75% - **$S_{cV}O_2$ и Lac удовлетворяли целевым.**
- У ~75% - исходные ЦВД и АДср не представлены.
- Недостаточно данных об:
  - **Исходной сравнимости групп;**
  - **Идентичности терапии в период исследования.**

6S-Trial критика

- Достаточно свидетельств использования HES вне рекомендаций изготовителя:
  - Безопасность HES у септических больных?
- Публикация в NEJM (!) уже влияет на использование HES в этой популяции больных.

6S-Trial критика

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ORIGINAL ARTICLE

N ENGL J MED 367;20 NEJM.ORG NOVEMBER 15, 2012

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST

METHODS

We randomly assigned 7000 patients who had been admitted to an intensive care unit (ICU) in a 1:1 ratio to receive either 6% HES with a molecular weight of 130 kD and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride or 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomization. The primary outcome was death within 90 days. Secondary outcomes included acute kidney injury and failure and treatment with renal-replacement therapy.

Коллоиды – нет

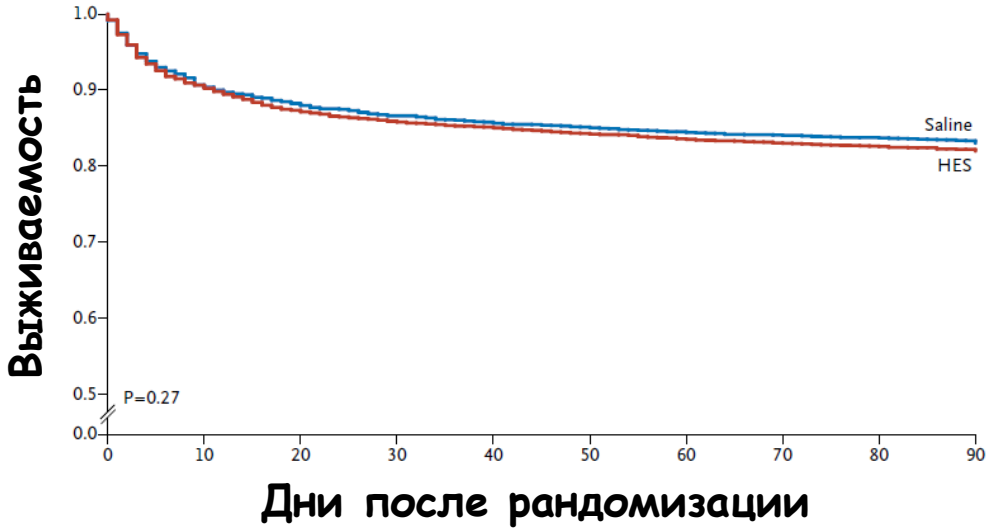
ORIGINAL ARTICLE

N ENGL J MED 367;20 NEJM.ORG NOVEMBER 15, 2012

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

CHEST

	90-day Mortality	Renal Replacement Tx	Renal Injury	Renal Failure	Adverse Events
HES (6%, 130/0.4)	18% (597/3315)	7%	34.6%	10.4%	5.3%
Saline (0.9%)	17% (566/3336)	5.8%	38%	9.2%	2.8%
P-value	0.26	**0.04**	**0.005**	0.12	**<0.001**



Летальность

- Нет отличий (90 дней)
- В т.ч. и в подруппах
  - ОПН
  - Сепсис
  - Травма
  - ЧМТ
  - APACHE II
  - HES до рандомизации

Myburgh JA, et al. *N Engl J Med*. 2012 Oct 17. [Epub ahead of print]

Коллоиды – нет

Intensive Care Med (2012) 38:368–383
DOI 10.1007/s00134-012-2472-9

SPECIAL ARTICLE

Konrad Reinhart
Anders Perner
Charles L. Sprung
Roman Jaeschke
Frederique Schortgen
A. B. Johan Groeneveld
Richard Beale
Christiane S. Hartog

Received: 3 January 2012
Accepted: 5 January 2012
Published online: 10 February 2012

Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients

- Рекомендуем **не использовать HES ≥200 kDa** и/или **DS >0.4** у пациентов с тяжелым сепсисом или риском повреждения почек и
- Предлагаем **не использовать 6% HES 130/0.4** или желатины в этой популяции
- …

Intensive Care Med (2012) 38:1556–1557
DOI 10.1007/s00134-012-2639-4

CORRESPONDENCE

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Comments on Reinhart et al.: consensus statement of the ESICM task force on colloid volume therapy in critically ill patients

Accepted: 15 June 2012
Published online: 25 July 2012

of Intensive Care Medicine's task force on colloid volume replacement in critically ill patients immediately raises two questions: what is the basis on which the task force was selected? Which entity initiated this initiative? The methodology of the article does not provide any information on these points, and the reader is left with some degree of doubt on how the individual members of the "task force" were selected. Eight individuals ("the eight panel members") apparently voted on each aspect of the statement. However, it seems highly questionable whether a small group of only eight individuals are capable of representing a true consensus of the various opinions among experts in the field in Europe—particularly when the group included two authors from the same department, representing 25 % of the votes.

Our concern is not whether the statement is correct or incorrect, but rather whether the approach used to establish the consensus was the most suitable one and whether it was capable of representing the opinions of intensivists throughout Europe—particularly since current data on the topic are limited, and several trials currently in progress are likely to provide new data in the very near future. Was the methodology for drawing up guidelines on best medical practices—as recommended by the European Health Committee (Comité Européen de la Santé, CDSP) and adopted by the Committee of Ministers of the Council of Europe in 2001 [2]—followed during the review process and publication of the statement?

It is therefore very surprising that such an important statement was apparently accepted for publication by *Intensive Care Medicine* within 2 days of submission (as specified on p. 368). In the absence of any information on how the present recommendations were evaluated, the reader can only speculate on the peer review process regarding this consensus statement. Are these recommendations supported by the majority of European intensive care specialists or do they merely reflect the "expert opinion" of eight authors?

Here, we suggest that these points need to be clarified. In future comparable cases, we would also recommend that such statements should be based on the input of representatives of all of the disciplines involved in critical care medicine (surgery, anesthesia, internal medicine, neurology, physiology, etc.). Such an approach, based on a comprehensible procedure, is currently being used in Germany to develop a guideline on intravascular volume therapy in adults, in accordance with the guidelines of the Working Group of Scientific Medical Specialist Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF) [3].

References

1. Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Groeneveld ABJ, Beale R, Hartog CS (2012) Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med 38:368–383

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КРАХМАЛЫ И ФУНКЦИЯ ПОЧЕК

КРАХМАЛЫ И ФУНКЦИЯ ПОЧЕК

- 316 детей (новорожденные – 12 лет)
- Все виды хирургии, в т.ч. ССХ
- Объем инфузии 11±4.8 $ml \cdot kg^{-1}$ (5–42)

Заключение

1. Умеренные дозы помогают сохранять стабильность гемодинамики…
2. Вероятность серьезных побочных эффектов <1%.
3. **Безопасен и эффективен** в т.ч. у новорожденных с нормальной функцией почек

Paediatr Anaesth. 2008 Oct;18(10):929-33.

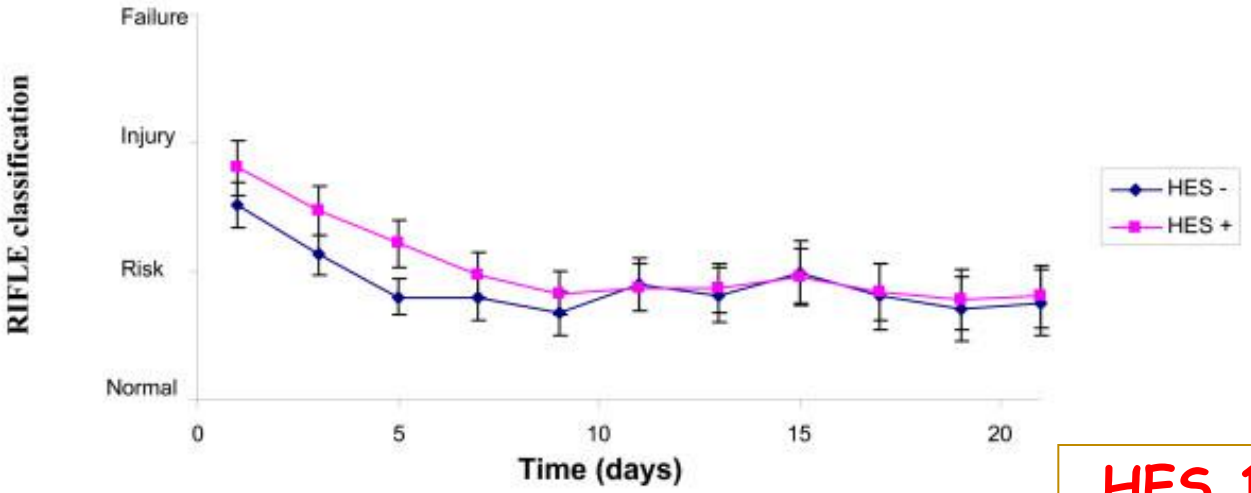
Hydroxyethyl starch 130/0.42/6:1 for perioperative plasma volume replacement in children: preliminary results of a European Prospective Multicenter Observational Postauthorization Safety Study (PASS).

Sümpelmann R, Kretz FJ, Gäbler R, Luntzer R, Baroncini S, Osterkorn D, Haeger MC, Osthaus WA.

Да

КРАХМАЛЫ И ФУНКЦИЯ ПОЧЕК

METHODS: This observational retrospective study included 363 patients hospitalized for more than 72 hours in our ICU. A hundred and sixty eight patients received HES during their stay and 195 did not.



HES 130/0.4 не вызывает ОПН, хотя объемы были малы (763±593 мл/48 ч)

Crit Care. 2010;14(2):R40.

Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury.

Boussekey N, Darmon R, Langlois J, Alfandari S, Devos P, Meybeck A, Chiche A, Georges H, Leroy O.

Да

КРАХМАЛЫ И ФУНКЦИЯ ПОЧЕК

- Большие дозы тетра-ГЭК
  - Нет доказательств негативного влияния
- Сепсис?
  - Взвесить риск/преимущества ГЭК

Dart et al., Cochrane Collaboration, 2010

Да

КРАХМАЛЫ И ФУНКЦИЯ ПОЧЕК

ГЭК (130/0.4) - 118 чел. ≈46 mL/kg, Σ≈649 mL/kg
Желатины - 87 чел. ≈43 mL/kg, Σ≈525 mL/kg
Кристаллоиды - 141 чел. Σ≈355 mL/kg

- Летальность ОРИТ/госпитальная равна:
  - ГЭК - 35/43%
  - Желатины – 26/31%
  - Кристаллоиды - 30/37%

Кристаллоиды:

1. Одинаково эффективны
2. Больший «+» баланс только в первые 2 дня
3. Реже повреждают почки

Crit Care Med. 2011 Jun;39(6):1335-42.

Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison.

Bayer O, Reinhart K, Sakr Y, Kabisch B, Kohl M, Riedemann NC, Bauer M, Settmacher U, Hekmat K, Hartog CS.

Нет?

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Crit Care Med. 2012 Feb;40(2):709-10; author reply 710-1. doi: 10.1097/CCM.0b013e31823b8b31.

Quantity may be more important than type of intravenous fluid.

Silversides JA, Ferguson AJ.

Comment on

Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. [Crit Care Med. 2011]

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Нет?

НЕ ЧТО, А СКОЛЬКО!

Mean daily fluid balance among 60-day survivors and non-survivors with acute renal failure (ARF), stratified by time of onset

Mean fluid balance, L/24 hours	Survivors	Non-survivors	*P* value
ARF	0.15 ± 1.06	0.98 ± 1.50	<0.001
Early ARF (occurring within 2 days of ICU admission)	0.14 ± 1.05	1.19 ± 1.48	<0.001
Late ARF (occurring more than 2 days after ICU admission)	0.11 ± 1.03	0.39 ± 1.40	0.06

Research

Critical Care 2008, **12**:R74 (doi:10.1186/cc6916)

Open Access

A positive fluid balance is associated with a worse outcome in patients with acute renal failure

Didier Payen[1], Anne Cornélie de Pont[2], Yasser Sakr[3], Claudia Spies[4], Konrad Reinhart[3], Jean Louis Vincent[5] for the Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators

Crit Care Med. 2012 Feb;40(2):709-10; author reply 710-1. doi: 10.1097/CCM.0b013e31823b8b31.

Quantity may be more important than type of intravenous fluid.

Silversides JA, Ferguson AJ.

Comment on

Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. [Crit Care Med. 2011]

НЕ ЧТО, А СКОЛЬКО!

- **Сердечная недостаточность:** венозный застой, а не малый выброс связан с дисфункцией почек

  Mullens W, Abrahams Z, Francis GS, et al:. *J Am Coll Cardiol, 2009.*

- **Септический шок:**
  - Большие ЦВД и положительный баланс - повреждение почек

    Boyd JH, Forbes J, Nakada TA, et al. *Crit Care Med, 2011;*

    Grams ME, Estrella MM, Coresh J, et al. *Clin J Am Soc Nephrol, 2011.*

- Т.е., это исследование снова подтверждает …

Crit Care Med. 2012 Feb;40(2):709-10; author reply 710-1. doi: 10.1097/CCM.0b013e31823b8b31.

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НЕ ЧТО, А СКОЛЬКО!

- **Сердечная недостаточность:** венозный застой, а не малый выброс связан с дисф

  Mullens W, Abrahams Z, F

- **Септический шок:**
  - Большие ЦВД и положительный ба

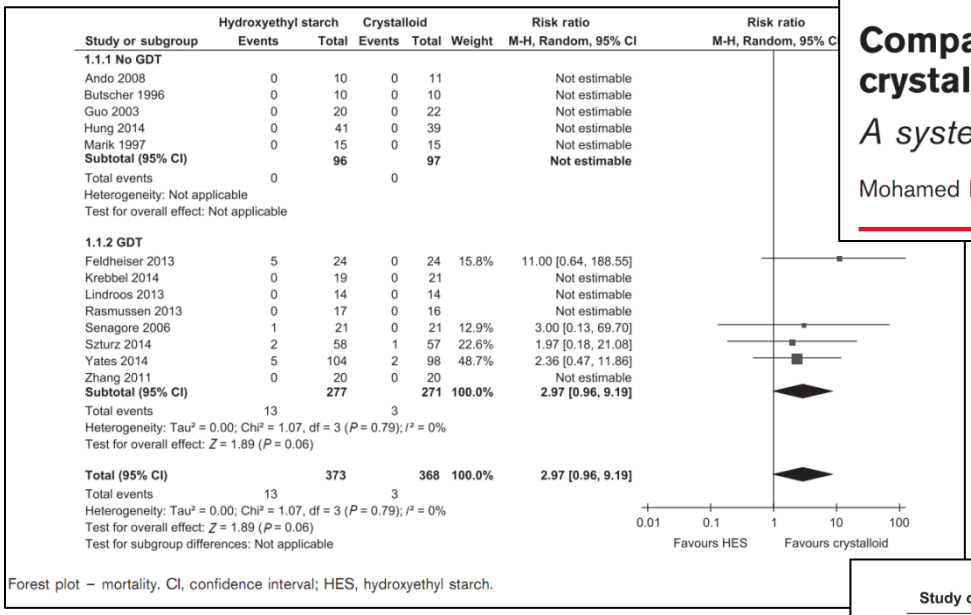
    Boyd JH, Forbes

    Grams ME, Estrella MM, Cor

- Т.е., это исследование

The authors reply:

We thank the authors Silversides and Ferguson for their interesting comments..



Forest plot – mortality. CI, confidence interval; HES, hydroxyethyl starch.

EJA

Eur J Anaesthesiol 2016; **33**:42–48

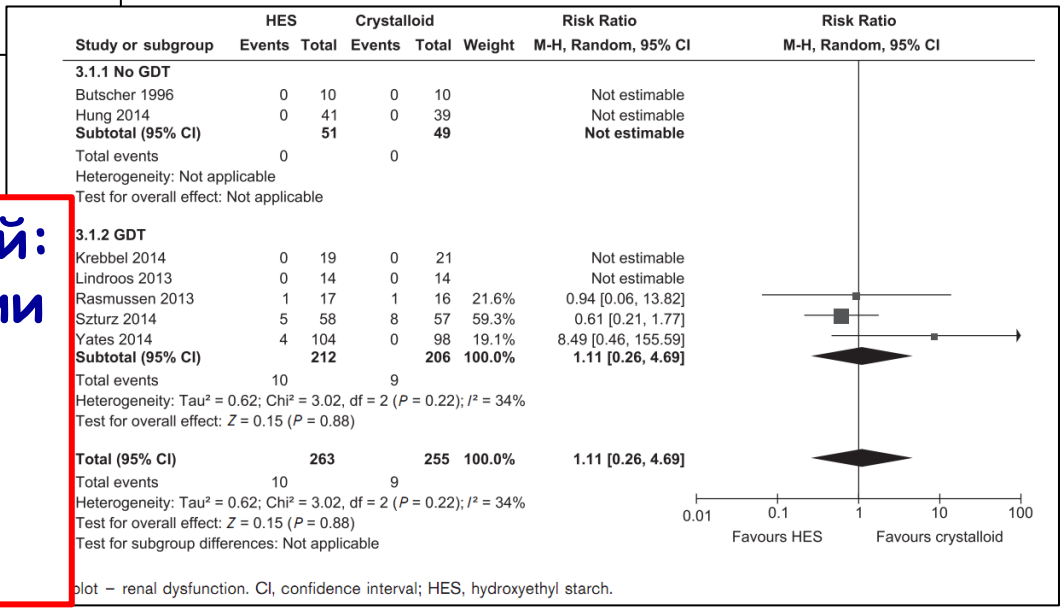
ORIGINAL ARTICLE

Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients

A systematic review and meta-analysis

Mohamed Raiman, Colin G. Mitchell, Bruce M. Biccard and Reitze N. Rodseth

Мета-анализ, 13 исследований: недостаточно данных о влиянии ГЭК на летальность, ОПН и тяжелые инфекции у некардиохирургических пациентов.



plot – renal dysfunction. CI, confidence interval; HES, hydroxyethyl starch.

EJA

Eur J Anaesthesiol 2016; **33**:1–2

CORRESPONDENCE

Crystalloids and hydroxyethyl starches in noncardiac surgical patients

Maria J. Colomina, Misericordia Basora, Vicky Moral and Juan V. Llau

- **Растворы ГЭК:**
  - Недостаточно данных для определения всех побочных эффектов;
  - Безопасны у некардиохирургических больных вместо желатинов или альбумина.

EJA

Eur J Anaesthesiol 2016; **33:**483–487

INVITED COMMENTARY

The quest for the holy volume therapy

Edoardo De Robertis, Arash Afshari and Dan Longrois

- **Растворы ГЭК:**
  - Хороши или плохи - нет убедительных доказательств.
  - Можно ожидать смену направления до 180° в клинической практике.

EJA

Eur J Anaesthesiol 2016; **33:**1–34

OPEN

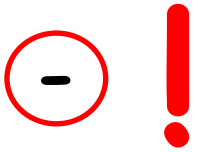
GUIDELINES

Intravascular volume therapy in adults

Guidelines from the Association of the Scientific Medical Societies in Germany

Gernot Marx, Achim W. Schindler, Christoph Mosch, Joerg Albers, Michael Bauer, Irmela Gnass, Carsten Hobohm, Uwe Janssens, Stefan Kluge, Peter Kranke, Tobias Maurer, Waltraut Merz, Edmund Neugebauer, Michael Quintel, Norbert Senninger, Hans-Joachim Trampisch, Christian Waydhas, Rene Wildenauer, Kai Zacharowski and Michaela Eikermann

Recommendation 4a-1 **GoR**



- **При острой периоперационной гиповолемии *кристаллоиды эквиваленты 6% HES или желатину***

МОДЕЛЬ С ГЛИКОКАЛИКСОМ

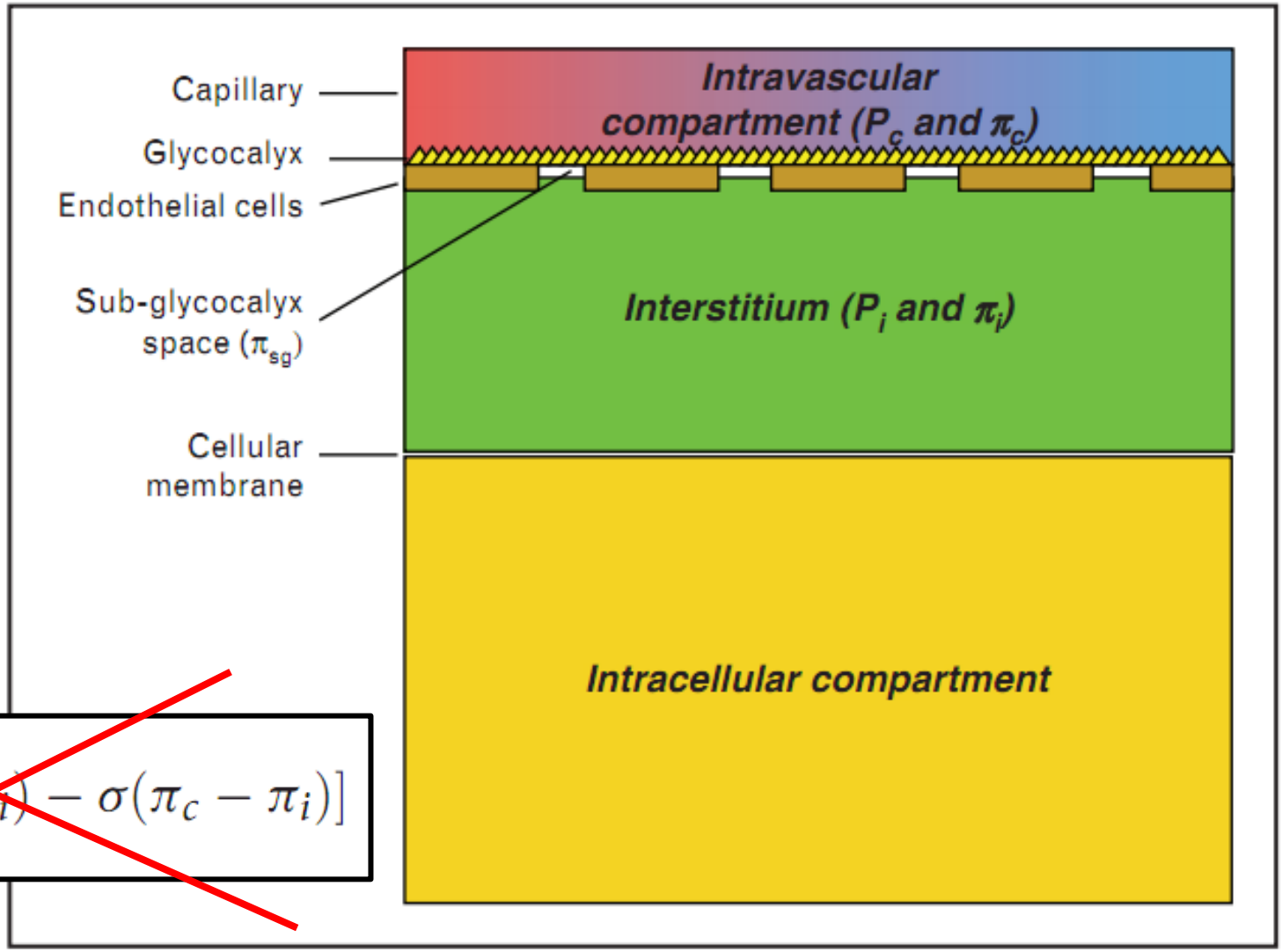
REVIEW

Luca Zazzeron[a], Luciano Gattinoni[b], and Pietro Caironi[a,c]

CURRENT OPINION

Role of albumin, starches and gelatins versus crystalloids in volume resuscitation of critically ill patients

Curr Opin Crit Care 2016, 22:000–000



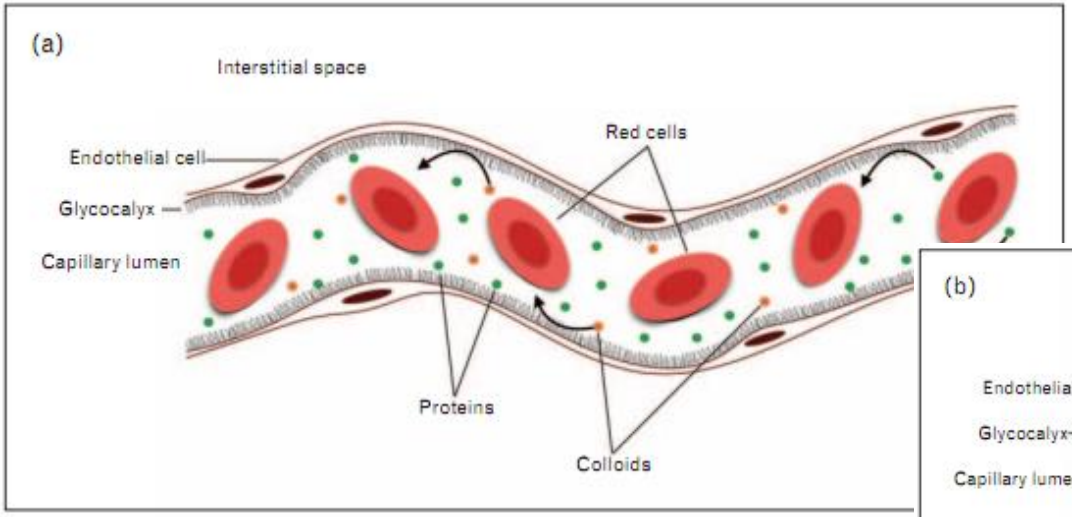
$$\frac{J_v}{A} = L_p[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

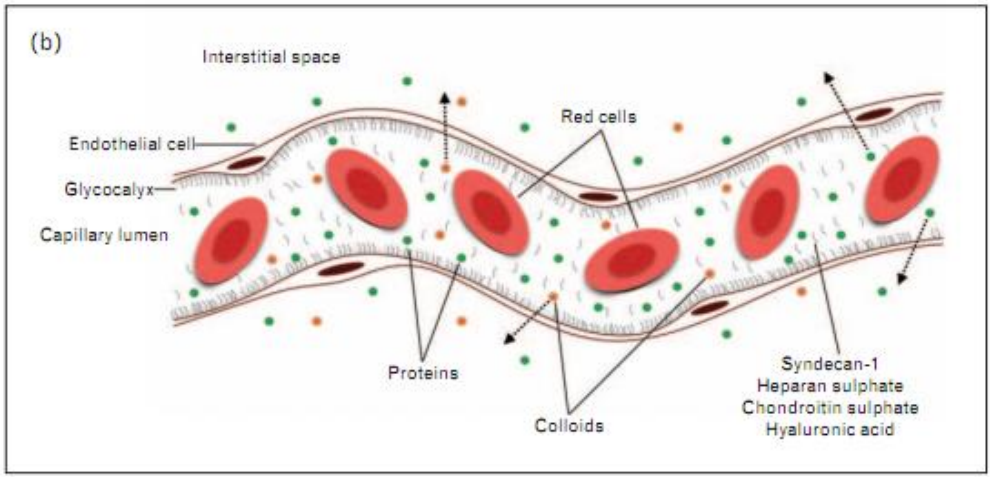
REVIEW
Luca Zazzeron[a], Luciano Gattinoni[b], and Pietro Caironi[a,c]
Role of albumin, starches and gelatins versus crystalloids in volume resuscitation of critically ill patients
Curr Opin Crit Care 2016, 22:000–000

МОДЕЛЬ С ГЛИКОКАЛИКСОМ

- **Объем – 700-1700 мл;**
- **Толщина:**
  - Капилляры – 0.2-2 μm;
  - Крупные сосуды – 8 μm.

Chappell D, Jacob M, et al. // Circulation Research, 2009





«Контекстно-чувствительный объемный эффект»

ВОЛЕМИЧЕСКОЕ СОСТОЯНИЕ ПАЦИЕНТА – ОПРЕДЕЛЯЕТ ПЛАЗМОЭКСПАНДЕРНЫЙ ЭФФЕКТ РАСТВОРА

Rehm M, Haller M, Orth V et al. Anesthesiology 2001.

Chappell D, Jacob M. Role of the glycocalyx in fluid management: small things matter. *Best Pract Res Clin Anaesthesiol* 2014.

EJA

Eur J Anaesthesiol 2016; **33:**1–34

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Recommendation 4a-2 4b-4 **GoR** **B**

- **Сбалансированные кристалл/коллоиды периоперационно и в ОРИТ**

REVIEW

Luca Zazzeron[a], Luciano Gattinoni[b], and Pietro Caironi[a,c]

CURRENT OPINION

Role of albumin, starches and gelatins versus crystalloids in volume resuscitation of critically ill patients

Curr Opin Crit Care 2016, 22:000–000

- «Теоретически, идеальный плазмозаменитель – цельная кровь, однако, это вряд ли осуществимо».

REVIEW

Luca Zazzeron[a], Luciano Gattinoni[b], and Pietro Caironi[a,c]

CURRENT OPINION

Role of albumin, starches and gelatins versus crystalloids in volume resuscitation of critically ill patients

Curr Opin Crit Care 2016, 22:000–000

- **Использование желатинов менее вредно, чем других синтетических коллоидов, хотя …они плохо изучены!**

А только желатины?

Мета-анализ 40 РКИ (3275 пац.)

Средние дозы 17 мл/кг (6-57 мл/кг)

Время наблюдения ≤24 ч

Разные пациенты, в т.ч. новорожденные

Заключение: несмотря на 60-летнюю практику, эффективность и безопасность невозможно оценить. Но… следует это сделать.

Intensive Care Med. 2012 Jul;38(7):1134-42.

Safety of gelatin for volume resuscitation--a systematic review and meta-analysis.

Thomas-Rueddel DO, Vlasakov V, Reinhart K, Jaeschke R, Rueddel H, Hutagalung R, Stacke A, Hartog CS.

Желатины

Препарат*	4%	3%
Концентрация, г/л	40	30
КОД, *мм* рт.ст.	34	25,5
Длительность циркуляции	4-5 *ч*	3-4 *ч* Через 2 *ч* в крови остается 20% препарата

* Инструкции по медицинскому применению препаратов

Гелофузин

Максимальная суточная доза

Практически зависит от степени достигнутой гемодилюции. Падение гематокрита ниже 25% (у пациентов с сердечно-сосудистой и легочной недостаточностью - 30%) требует переливания эритроцитарной массы или цельной крови, после чего введение Гелофузина можно продолжить. При массивных кровопотерях, в случае необходимости, возможно переливание до 10-15 л раствора в сутки (при соблюдении указанных выше условий).

Побочные действия:

Анафилактоидные реакции, при массивном введении - гипокоагуляция (вызванная эффектом разведения).Передозировка. Симптомы: гемодилюция.

Chappell and Jacob *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2013, **21**:61
http://www.sjtrem.com/content/21/1/61

SCANDINAVIAN JOURNAL OF
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COMMENTARY Open Access

Hydroxyethyl starch - the importance of being earnest

Daniel Chappell and Matthias Jacob*

Abstract

Despite ongoing controversial expert discussions the European Medicines Agency (EMA) recently recommended to suspend marketing authorisations for hydroxyethyl starch. This comment critically evaluates the line of arguments. Basically, the only indication for a colloid is intravascular hypovolemia. Crystalloid use appears reasonable to compensate ongoing extracellular losses beyond. In the hemodynamically instable patient this leads to the distinction between an initial *resuscitation phase* where colloids might be indicated and a crystalloidal *maintenance phase* thereafter. It is important to bear this in mind when reevaluating the studies the EMA referred to in the context of its recent decision: i) VISEP compared ringer's lactate to 10% HES 200/0.5 in septic patients and found an increased incidence of renal failure in HES receivers. Unfortunately, study treatment was started only after initial stabilization with HES, randomizing hemodynamically stable patients into a rational (crystalloids) and an irrational (high dose starch until ICU discharge) maintenance treatment. ii) 6S compared ringer's acetate to 6% HES 130/0.42 for fluid resuscitation in septic patients and found an increased need of renal replacement therapy and a higher mortality in the HES group. However, patients of both groups were again randomized only after initial stabilization with colloids, the actual comparison was, therefore, again rational vs. irrational. Beyond that, the documentation is partly fragmentary, leaving many important questions around the fate of the patients unanswered. iii) CHEST randomized ICU patients to receive saline or 6% HES 130/0.4 for fluid resuscitation. Actually, despite partly discussed in a different way, this trial showed no relevant differences in outcome.

In all, two studies showed what happens to septic patients if starches are used in a way we do not observe in daily practice. The third one actually proves their safety. The benefit of perioperative goal-directed preload optimization using starches is unquestioned. Taking these informations into account, the recommendation of the EMA starches to be generally dangerous remains mysterious and incomprehensible. An authority being able to dictate behavior should stand clear from oppressively ending a worldwide expert discussion and step back into the role of the observer until science achieves an agreement.

Keywords: Colloids, Crystalloids, Fluid therapy, Hydroxyethyl starch, Sepsis

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рандомизация **ПОСЛЕ** ***стабилизации гемодинамики*** коллоидами, в т.ч. ГЭК

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  - CHEST (0.9% NaCl/6% ГЭК 130/0.4 - **НЕТ** отличий в исходах), где инфузия **ДЛЯ** ***стабилизации гемодинамики***

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- Т.е., 2 исследования – демонстрация того, что случается с септическим пациентом в ситуации… …не наблюдаемой в рутинной практике
- А 3-е – демонстрирует безопасность крахмалов
- Преимущества ГЭК для периоперационной целенаправленной оптимизации преднагрузки не обсуждаются

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- Т.о. – рекомендации EMA об опасности ГЭК…

ЗАГАДОЧНЫ и НЕПОСТИЖИМЫ

- Диктующим поведение инстанциям следует:
  - Держаться в стороне до окончания дискуссии экспертов
  - Вернуться на позиции наблюдателя пока наука не достигнет соглашения

Abstract

Despite ongoing controversial expert discussions the European Medicines Agency (EMA) recently recommended to suspend marketing authorisations for hydroxyethyl starch solutions. Several arguments. Basically, the only indication for a colloid is intravascular hypovolemia. Crystalloid use appears reasonable to compensate ongoing extracellular losses beyond. In the hemodynamically instable patient this leads to the distinction between an initial *resuscitation phase* where colloids might be indicated and a crystalloidal *maintenance* in the context of its recent decision: i) VISEP compared ringer's lactate to 10% HES 200/0.5 in septic patients and found an increased incidence of renal failure in HES receivers. Unfortunately, study treatment was started only after initial stabilization with HES, randomizing hemodynamically stable patients into a rational (crystalloids) and an irrational (high dose starch until ICU discharge) maintenance treatment. ii) 6S compared ringer's acetate to 6% HES 130/0.42 for fluid resuscitation in septic patients and found an increased need of renal replacement therapy and a higher mortality in the HES group. However, patients of both groups were again randomized only after initial stabilization [illegible] partly fragmentary, leaving many important questions around the fate of the patients unanswered. iii) CHEST randomized ICU patients to receive saline or 6% HES 130/0.4 for fluid resuscitation. Actually, despite partly discussed in a different way, this trial showed no relevant differences in outcome.

In all, two studies showed what happens to septic patients if starches are used in a way we do not observe in daily practice. The third one actually proves their safety. The benefit of perioperative goal-directed preload optimization using starches is unquestioned. Taking these informations into account, the recommendation of the EMA starches to be generally dangerous remains mysterious and incomprehensible. An authority being able to dictate behavior should stand clear from oppressively ending a worldwide expert discussion and step back into the role of the observer until science achieves an agreement.

Keywords: Colloids, Crystalloids, Fluid therapy, Hydroxyethyl starch, Sepsis

Итак…

Коллоиды? Кристаллоиды?

Альбумин?

- Понятно, что:
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  - Многочисленные дефекты дизайнов
  - Интерпретация результатов может существенно различаться
  - …

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Итак…

Что? Сколько?

КОГДА!!

- **Волемия, выброс – коллоиды**
- **Гидратация – кристаллоиды**


ПРОФКОМ
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ПРЕДУПРЕЖДАЕТ
ПЕРЕД РАБОТОЙ
ПРОЧИТАЙ ИНСТРУКЦИЮ!

Итак…


Центр им. В.А. Алмазова
Федеральный
специализированный
перинатальный
центр

Спасибо!