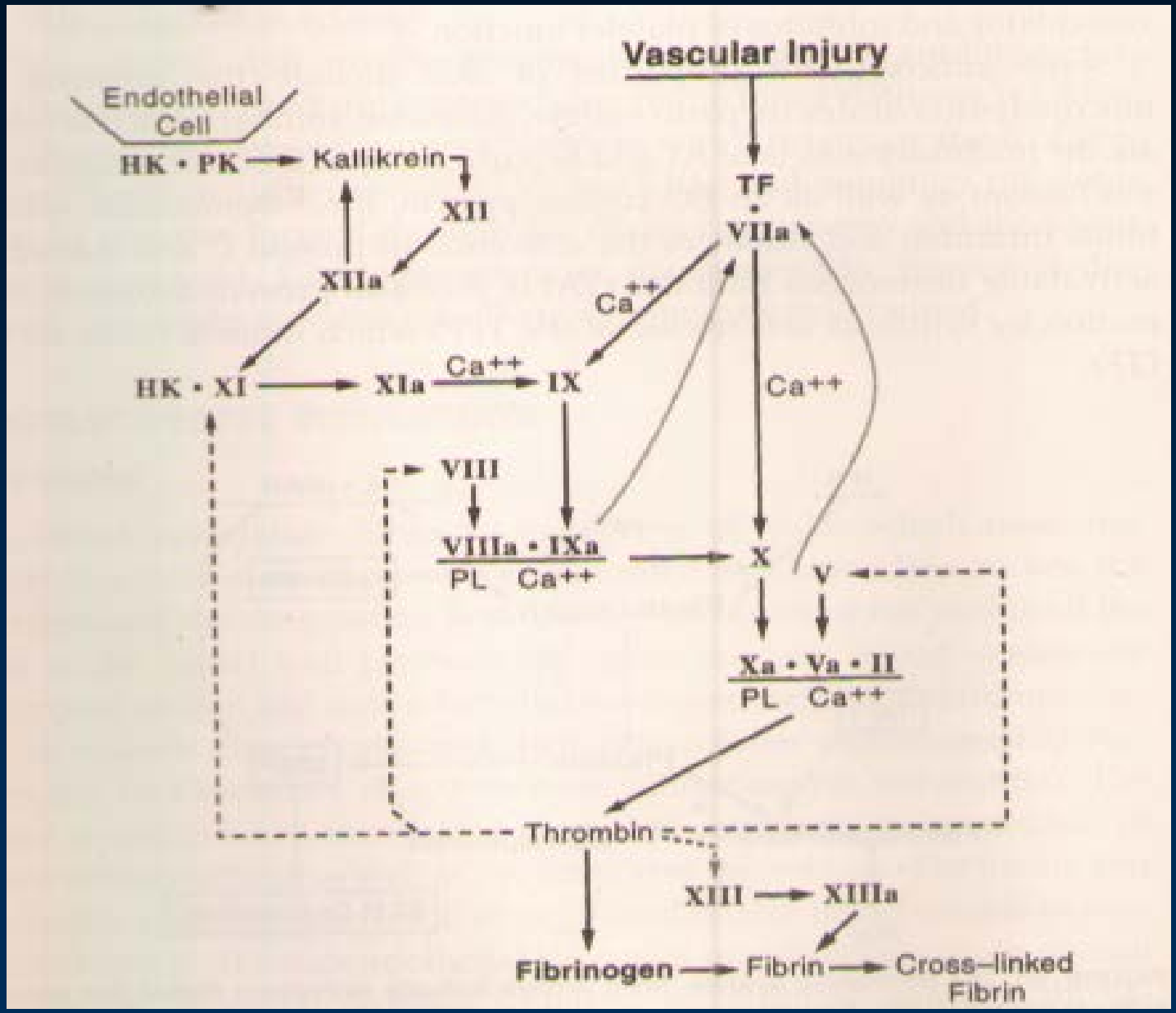
Применение фактора rVIIa в нейрохирургии

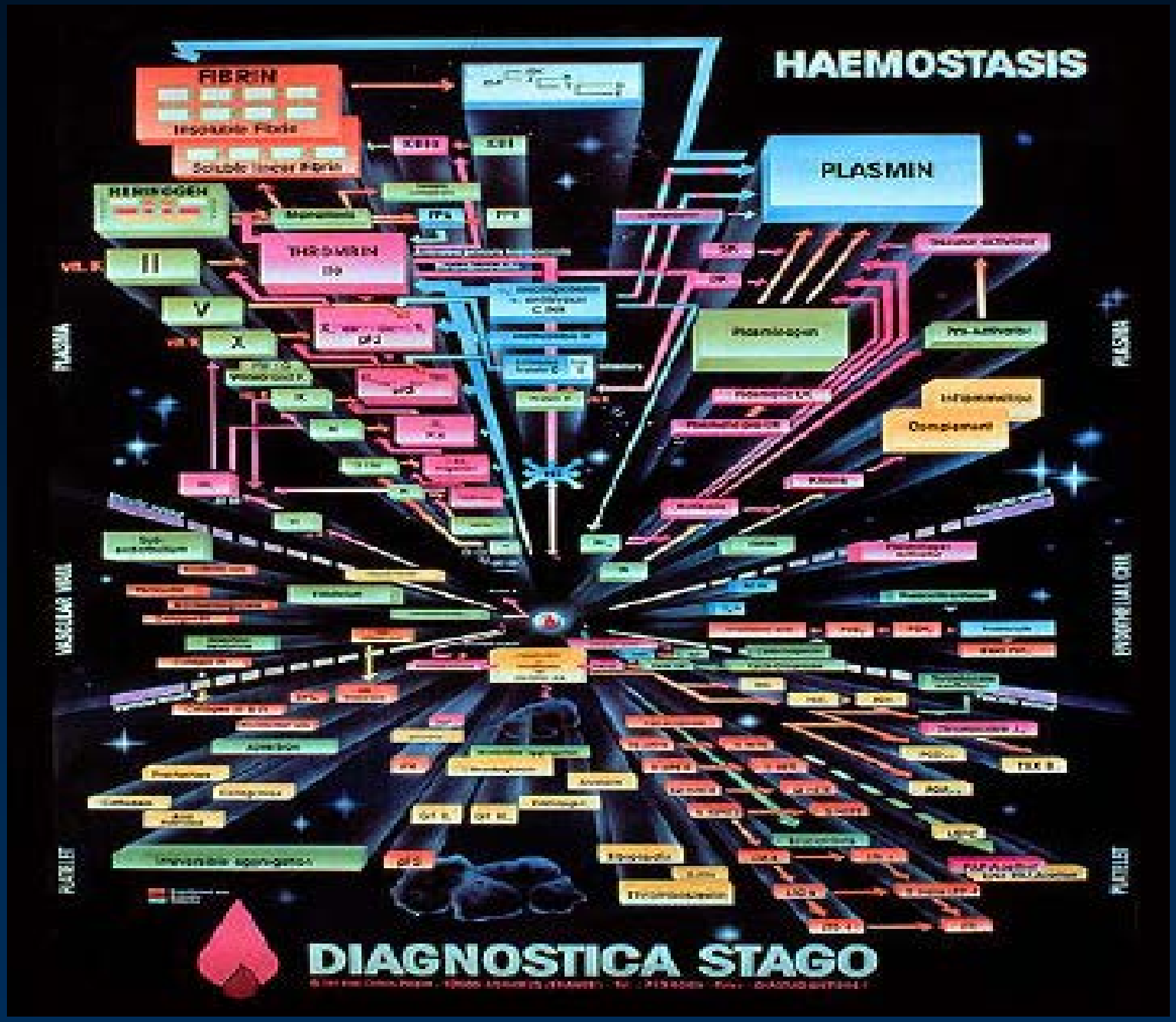
А.Ю. Лубнин, Н.В. Леменева
ННПЦ нейрохирургии им. Н.Н. Бурденко,
Москва, 2017

Интро

- Система гемостаза – одна из древнейших и наиболее надежных систем человеческого организма!
- Ее структура, с одной стороны, крайне проста и логична – свертывающая и противосвертывающая система, находящие в состоянии баланса, и позволяющие поддерживать жидкое состояние крови, но при необходимости, немедленное тромбообразование и остановку кровотечения. С другой стороны это архи сложная система, про которую мы до сих пор знаем далеко не все.

Система гемостаза





06. Гемостаз для чайников. Гемостаз: Норма и немного патологии... Л.Л. Кривский,2013

Интро

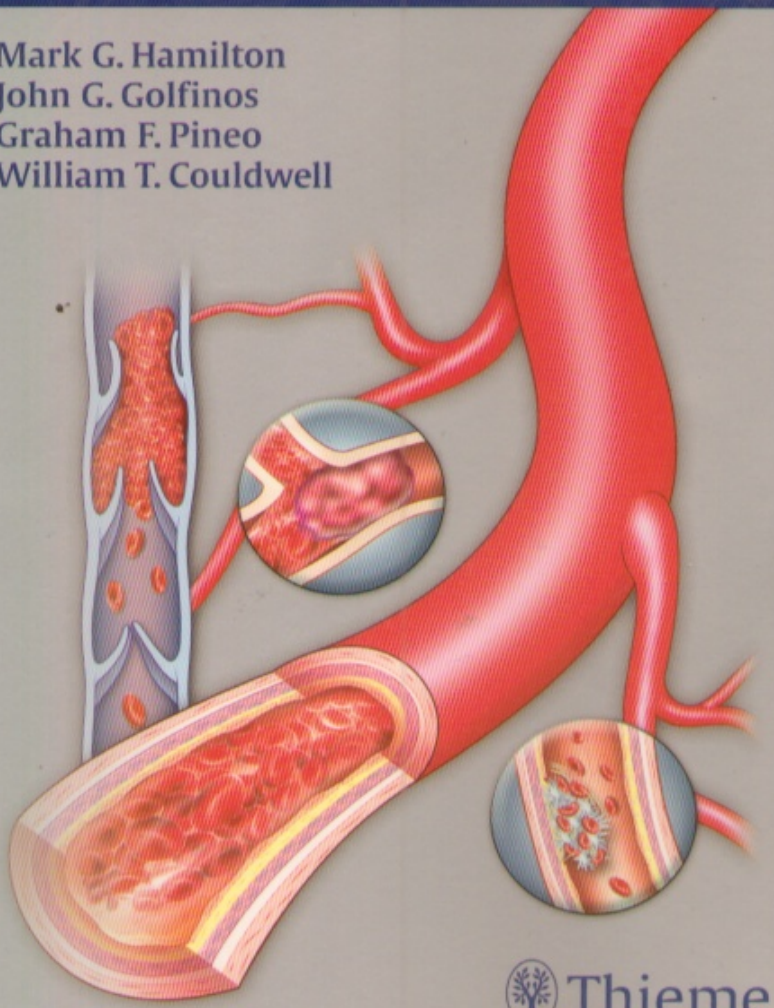
- Несмотря на тысячелетнюю эволюцию и исключительную надежность система гемостаза все же иногда дает сбой.
- Это может быть следствием врожденных проблем (гемофилии, болезнь Фон Виллибрадта, тромбофилии) или приобретенных состояний (прием антикоагулянтов, дезагрегантов или иных препаратов).
- Отсюда два важнейших клинических проявления нарушений в системе гемостаза – повышенная кровоточивость или наоборот повышенная склонность к тромбообразованию. Оба могут стать причиной неблагоприятного исхода у нейрохирургического больного.

Интро

- Специфика нейрохирургических больных такова, что нарушения в системе гемостаза для них имеют жизненно важное значение.
- Гипокоагуляция (ведущий причинный фактор) связана с реальным риском такого жизнеугрожающего осложнения как формирование острой послеоперационной гематомы, летальность от которого при вмешательствах на ЗЧЯ может достигать 40 – 80 %!
- Гиперкоагуляция лежит в основе некоторых специфических проблем (например синус тромбоз) и конечно один из ведущих факторов ТГВ и ТЭЛА (нейрохирургические больные – группа высокого риска).

Handbook of Bleeding and Coagulation for Neurosurgery

Mark G. Hamilton
John G. Golfinos
Graham F. Pineo
William T. Couldwell

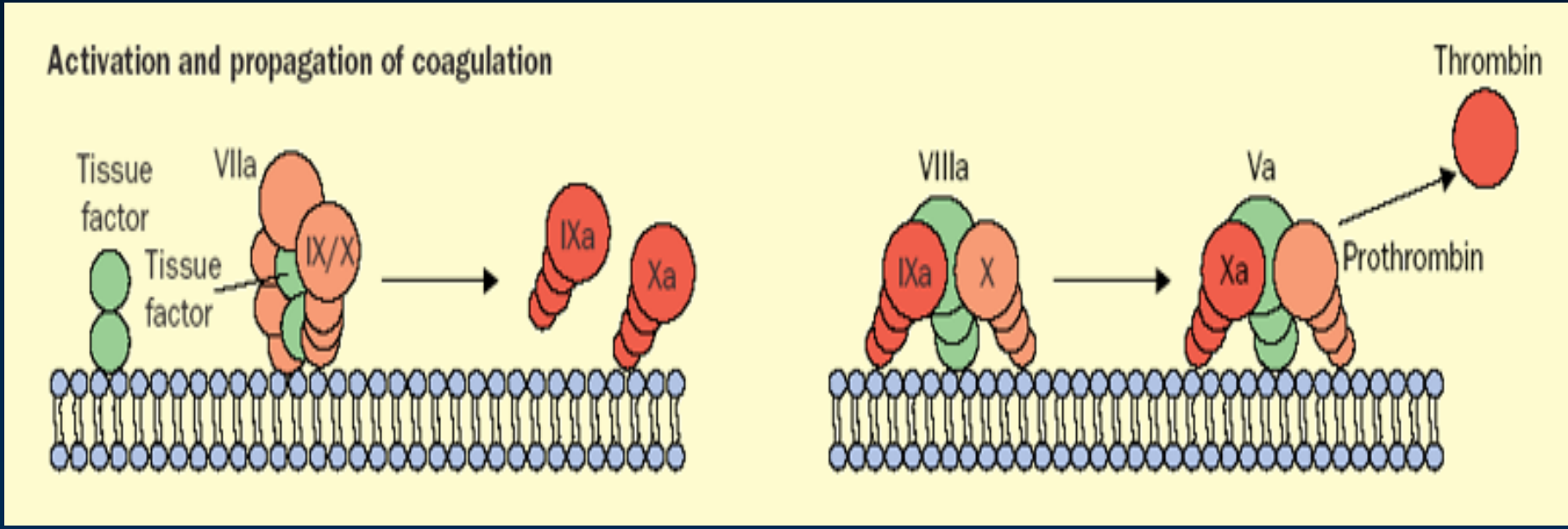


Thieme

Фактор VII и рекомбинантные технологии

- Впервые активированный фактор VII, полученный из плазмы, был использован клинически у 2 больных с ингибиторной формой гемофилии в начале 80х прошлого века для остановки кровотечения. Эффект был положительным, гемостаз был достигнут. Но получить его таким способом в достаточных количествах оказалось невозможным.
- Поэтому были использованы рекомбинантные технологии (например, генно-инженерные технологии из клеток яичников хомячков). В конце 80х датская компания «Ново Нордиск» синтезировала и провела первые клинические испытания препарата НовоСевен.

Схема действия VIIa



Механизм действия

- Клетки сосудистой стенки, содержащие тканевой фактор, в случае повреждения контактируют с плазмой в результате чего образуется комплекс между тканевым фактором и фактором VII-VIIa. Последний активирует факторы X и IX, а фактор Xa в сочетании с фактором Va конвертируют небольшое начальное количество протромбина в тромбин. Этот начальный тромбин связывает и активирует тромбоциты. После чего происходит «тромбиновый взрыв» – массивная генерация тромбина. И далее фибриноген в фибрин, но высокая концентрация тромбина делает этот фибриновый сгусток прочным для лизиса. Но есть и другие механизмы.

Фактор VII и рекомбинантные технологии

- С 1996 г. (пострегистрационное использование) по 2004 г. в мире было использовано более 700000 стандартных доз препарата (90 мкг/кг).
- С 1999 г. препарат НовоСевен был официально разрешен FDA для лечения больных гемофилией в США. Позднее и при некоторых тромбоцитопатиях.
- В 2009 г. ЗАО «Генериум» в России синтезировала био-аналог препарата НовоСевен – препарат Коагил VII.
- Гемостатический эффект препарата Коагил VII в настоящее время доказан в серии отечественных исследований и в одном сравнительном.

Фактор VII и рекомбинантные технологии

- *Вдовин В.В., Наместников Ю.А., Свирин П.В., и др. Тест генерации тромбина в лабораторном контроле эффективности терапии тромбастении Гланцмана препаратом Коагил – VII. // Вопросы гематологии, онкологии и иммунопатологии в педиатрии. 2010. № 3 стр. 41 – 44.*
- *Зоренко В.Ю., Полянская Т.Ю., Галстян Г.М., и др. Опыт применения препарата Коагил - VII при ортопедических операциях у больных с ингибиторной гемофилией А. // Вопросы гематологии, онкологии и иммунопатологии в педиатрии. 2010. № 3 стр. 35 – 40.*
- *Тарасова И.С. Медицинская помощь больным с ингибиторной формой гемофилии. // Вопросы гематологии, онкологии и иммунопатологии в педиатрии. 2010. № 1 стр. 3 – 9.*
- *Зоренко В.Ю., Галстян Г.М., Полянская Т.Ю., и др. Сравнение гемостатического действия препаратов рекомбинантного активированного фактора свертывания крови VII. // Вопросы гематологии, онкологии и иммунопатологии в педиатрии. 2011. № 4 стр. 16 – 22.*

УДК 615.273.5.036.8

Сравнение гемостатического действия препаратов рекомбинантного активированного фактора свертывания крови VII

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Таблица 3. **Активность FVII в плазме, АЧТВ, ПВ и ЭТП до и после введения препаратов rFVIIa**

Параметр	Активность FVII, % от нормальной плазмы		АЧТВ, с		ПВ, с		ЭТП, нмоль х 90 мин	
Значение в норме	80–100		30–35		10–15		700–800	
Препарат	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен
До введения	97,0 ± 19,3	92,9 ± 22,4	119,0 ± 26,0	113,0 ± 37,0	11,4 ± 0,7	11,0 ± 0,7	633,8 ± 153,3	676,0 ± 161,2
Время после введения препарата:								
15 мин	3642,0 ± 1377,0*	3283,0 ± 787,1*	87,7 ± 6,9*	68,0 ± 9,5*	7,3 ± 0,3*	7,4 ± 0,2*	752,9 ± 181,6*	727,4 ± 161,1*
30 мин	2779,0 ± 612,5*	2862,0 ± 925,6*	68,6 ± 7,8*	73,3 ± 12,8*	7,4 ± 0,2*	7,4 ± 0,4*	760,8 ± 199,9*	730,9 ± 144,4*
1 ч	2160,0 ± 505,0*	1816,0 ± 836,7*	70,3 ± 9,0	76,9 ± 14,4	7,6 ± 0,3*	7,5 ± 0,4*	775,5 ± 154,5*	773,5 ± 100,8*
2 ч	1511,0 ± 515,9*	1170,0 ± 553,2*	75,4 ± 9,3*	79,5 ± 12,5	7,8 ± 0,6*	7,7 ± 0,5*	756,9 ± 177,5*	744,4 ± 140,0*
6 ч	521,9 ± 163,5*	383,2 ± 175,4*	89,0 ± 13,9*	90,5 ± 20,1*	8,3 ± 0,6*	8,8 ± 0,8*	758,5 ± 153,3*	754,4 ± 125,4*
9 ч	302,3 ± 93,9*	288,9 ± 99,0*	100,9 ± 20,7*	99,1 ± 22,4	9,0 ± 0,6*	9,5 ± 0,6*	745,2 ± 171,0*	730,3 ± 151,0*
12 ч	191,0 ± 79,9*	184,8 ± 73,9*	107,8 ± 19,6	113,5 ± 34,0	9,6 ± 0,6*	10,0 ± 6,5*	727,7 ± 160,0*	699,2 ± 161,2
24 ч	129,5 ± 38,5*	119,8 ± 34,5*	116,6 ± 21,6	118,5 ± 33,0	11,2 ± 0,7	10,0 ± 0,9	691,7 ± 153,8	692,9 ± 118,7
36 ч	107,4 ± 22,3*	107,4 ± 29,0*	117,5 ± 24,8	118,7 ± 30,5	11,5 ± 0,7	11,3 ± 0,7	667,9 ± 143,4	663,0 ± 152,1
48 ч	101,9 ± 24,0	100,5 ± 24,3*	117,6 ± 25,0	117,7 ± 29,2	11,1 ± 1,3	11,4 ± 0,7	676,0 ± 146,4	648,3 ± 138,3

**Статистически значимые различия (парный t-критерий Стьюдента; $p < 0,05$) по сравнению со значением параметра до введения препарата*

УДК 615.273.5.036.8

Сравнение гемостатического действия препаратов рекомбинантного активированного фактора свертывания крови VII

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Таблица 4. **Параметры ТЭГ до и после введения препаратов rFVIIa**

Параметр	*R*, мин		*K*, мин		Угол α, град.		*MA*, мм		*CI*	
Значение в норме	9–27		2–9		22–58		44–64		от –3 до 3	
Препарат	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен	Коагил-VII	НовоСэвен
До введения	Н.о. (34,0)	Н.о. (26,0)	Н.о. (7,6)	Н.о. (7,2)	Н.о. (26,0)	Н.о. (29,0)	Н.о. (43,0)	Н.о. (43,0)	Н.о. (–5,2)	Н.о. (–4,7)
Время после введения препарата:										
15 мин	28,0 ± 9,4	29,9 ± 22,1	9,2 ± 4,0	8,3 ± 4,8	30,9 ± 14,2	32,9 ± 14,8	46,1 ± 14,7	56,6 ± 13,3	–4,5 ± 3,0	–2,1 ± 1,9
30 мин	22,5 ± 7,2	31,3 ± 21,5	6,1 ± 2,3	10,1 ± 10,5	36,3 ± 12,0	32,0 ± 16,2	54,4 ± 12,6	56,1 ± 15,7	–3,2 ± 1,5	–2,5 ± 1,6
1 ч	20,8 ± 6,3	31,7 ± 7,2	5,8 ± 1,9	10,8 ± 4,5*	40,5 ± 13,6	26,3 ± 10,7	58,3 ± 7,1	52,4 ± 12,3	–2,6 ± 1,3	–3,2 ± 1,7
2 ч	35,1 ± 21,4	36,2 ± 21,1	9,6 ± 10,1	9,4 ± 4,8	35,4 ± 20,1	29,9 ± 14,0	47,1 ± 24,5	51,2 ± 19,0	–3,5 ± 2,5	–2,9 ± 1,9
24 ч	Н.о. (37,0)	Н.о. (61,0)	Н.о. (23,0)	Н.о. (40,0)	Н.о. (9,7)	Н.о. (5,5)	Н.о. (36)	Н.о. (25,0)	Н.о. (–4,6)	Н.о. (–8,6)
48 ч	Н.о. (36,0)	Н.о. (61,4)	Н.о. (22,0)	Н.о. (40,4)	Н.о. (8,3)	Н.о. (5,0)	Н.о. (39)	Н.о. (25,4)	Н.о. (–3,6)	Н.о. (–8,7)

*Н.о. – параметр у больных не определяется в связи с гипокоагуляцией, в скобках даны значения параметра у 1 больного (наблюдение №2); * – получены статистически значимые различия (парный t-критерий Стьюдента; $p < 0,05$) между группами пациентов, получивших препарат Коагил-VII и препарат НовоСэвен.*

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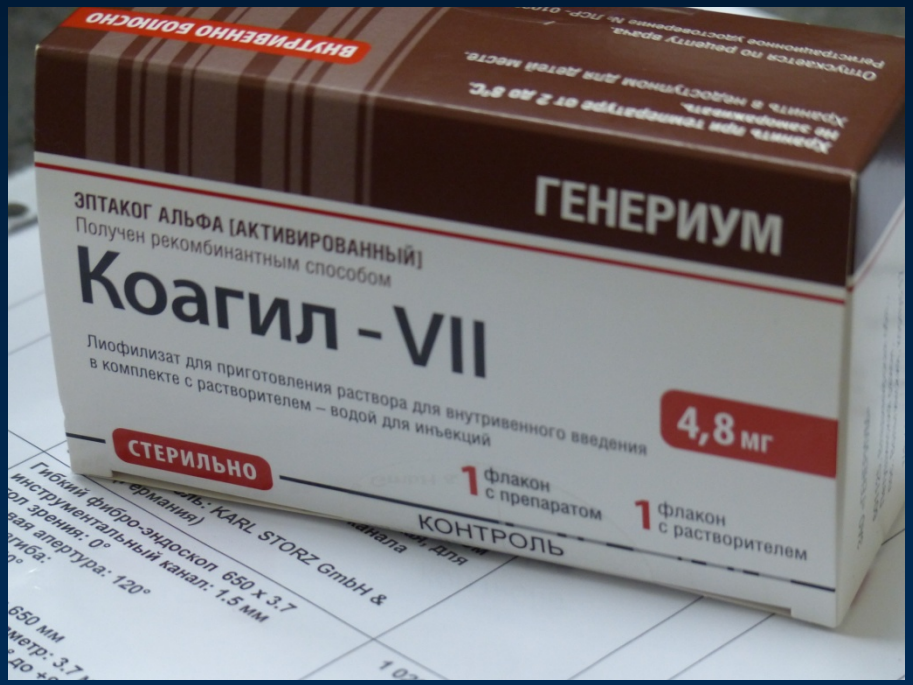
Таким образом, проведенное исследование показало, что изменения лабораторных показателей, свидетельствуют о том, что гемостатический эффект обоих препаратов rFVIIa (Коагил-VII и НовоСэвен) сопоставим как по выраженности, так и по длительности. Необходимо проведение дальнейших клинических исследований для сравнения клинической эффективности этих двух препаратов rFVIIa при лечении геморрагического синдрома у больных с ингибиторной формой гемофилии.

Препараты VII фактора



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REVIEW

Recombinant-activated coagulation factor VIIa (NovoSeven®): current development

R. B. Weiskopf

Novo Nordisk A/S, Novo Allé, DK-2880 Bagsvaerd, Denmark and Department of Anaesthesia, University of California, San Francisco, CA, USA

Vox Sanguinis

Recombinant activated coagulation factor VII (rFVIIa) was developed initially for treatment of patients with hemophilia and neutralizing antibodies ("inhibitors") to coagulation factors VIII or IX. Owing to the unique and selective mechanism of action of rFVIIa and encouraged by clinical experience with other circumstances of inadequate hemostasis, a broad development program has been pursued to test potential

Recombinant Activated Factor VII: Mechanisms of Action and Current Indications

Massimo Franchini, M.D.,[1] and Giuseppe Lippi, M.D.[2]

ABSTRACT

Recombinant activated factor VII (rFVIIa) was initially developed to overcome the limitations of existing treatments for patients with congenital hemophilia and inhibitors. Clinical success in this arena led to experimental use in other coagulopathies characterized by impaired thrombin generation, and approval for use in acquired hemophilia, factor VII deficiency, and Glanzmann's thrombasthenia soon followed. Extensive research and grow-

Коррекция гипокоагуляции, обусловленной потерей/дефицитом

- В/в инфузия свежезамороженной плазмы.
- В/в инфузия препаратов плазмы - крио-преципитата, фибриногена и отдельных факторов.
- Тромбоциты.
- Ингибиторы фибринолиза.
- Препарат rFVIIa.

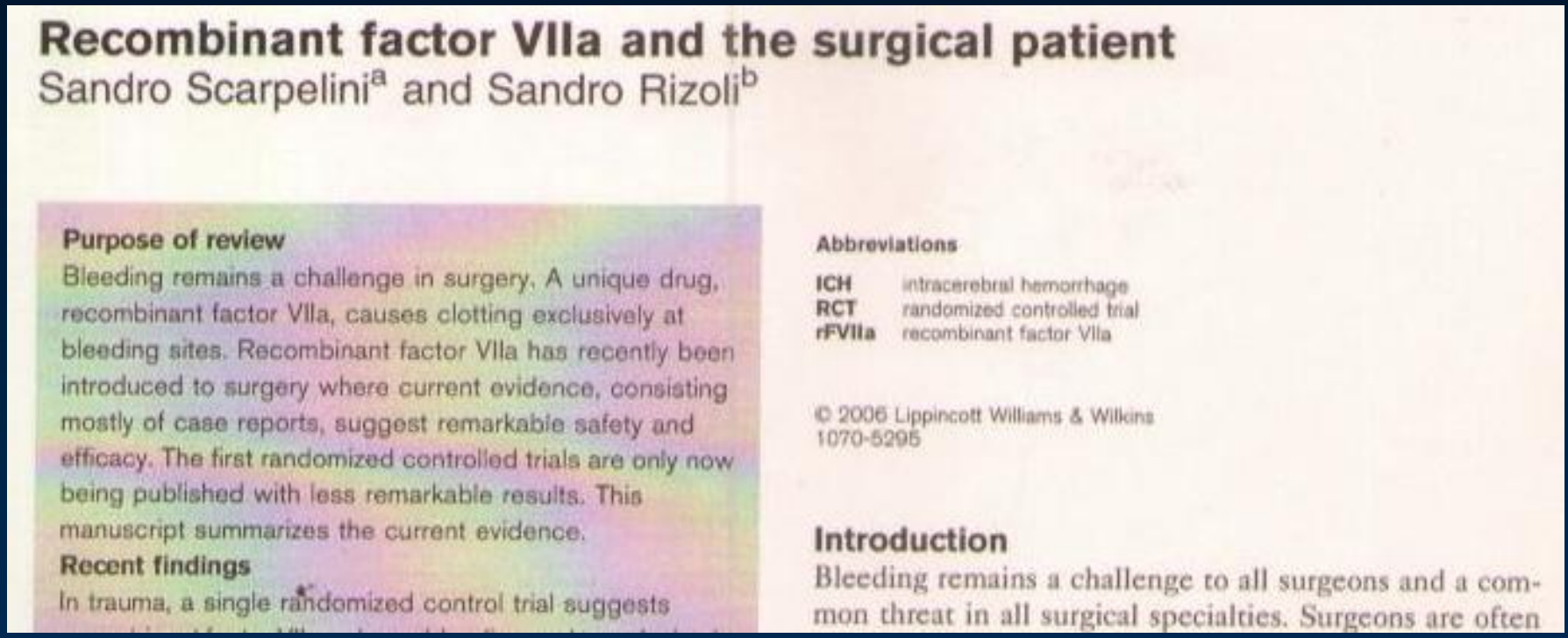
ПЕРЕЛИВАНИЕ ПЛАЗМЫ и ее препаратов - ЭТО

- Риск инфицирования реципиента.
- Риск перегрузки объемом.
- Риск развития анафилактических и иммунных (TRALI) реакций.
- Риск случайного переливания иногруппного компонента крови.
- Увеличение риска развития полиорганной недостаточности в рамках синдрома массивных трансфузий.

Активированный рекомбинантный VII фактор

- rVIIa не имеет этих недостатков.
- Запускает каскад свертывания только в месте повреждения тканей.
- Образующийся сгусток более устойчив к фибринолизу, чем обычный.

rVIIa в хирургии



Recombinant factor VIIa and the surgical patient

Sandro Scarpelini[a] and Sandro Rizoli[b]

Purpose of review

Bleeding remains a challenge in surgery. A unique drug, recombinant factor VIIa, causes clotting exclusively at bleeding sites. Recombinant factor VIIa has recently been introduced to surgery where current evidence, consisting mostly of case reports, suggest remarkable safety and efficacy. The first randomized controlled trials are only now being published with less remarkable results. This manuscript summarizes the current evidence.

Recent findings

In trauma, a single randomized control trial suggests

Abbreviations

ICH	intracerebral hemorrhage
RCT	randomized controlled trial
rFVIIa	recombinant factor VIIa

1070-5295

Introduction

Bleeding remains a challenge to all surgeons and a common threat in all surgical specialties. Surgeons are often

- Используется практически во всех областях хирургии с высоким риском массивной операционной кровопотери.

potential to transform surgical practice. Current evidence on the efficacy and safety of rFVIIa in surgery does not yet support its use as standard of care in surgery. RFVIIa also lacks evidence-based guidelines to direct its use for almost all proposed indications. Like all new drugs, rFVIIa still needs a lot more investigation in surgical bleeding.

Trauma surgery

About half of all early trauma deaths are due to hemorrhage and trauma patients consume massive amounts of blood products. Not surprisingly, trauma was the first area to explore rFVIIa outside hemophilia and is currently among the largest off-label users. It was Kenet's 1999 report of successfully using rFVIIa in a bleeding soldier that initiated worldwide interest in experimenting rFVIIa for non-hemophilia bleedings [5].

Numerous retrospective case reports and series followed this report, invariably describing very favorable outcomes, particularly among coagulopathic trauma patients [10,11,12•,13,14,15•]. The largest series in trauma described 81 coagulopathic patients in whom rFVIIa successfully reversed the coagulopathy in 75% [16]. This and other studies invariably report a remarkable efficacy in stopping hemorrhage but not of improving survival. There are also preclinical animal studies mimicking human trauma that describe excellent efficacy and safety [17]. Most case reports and case series have uniformly recommended that further studies are necessary before recommending that rFVIIa be routinely used in trauma.

The first and only trauma randomized controlled trial (RCT) was published in 2005 and included 301 patients, 143 blunt and 134 penetrating. The RCT design anticipated two final analyses, one including all patients and another excluding early deaths, those patients with unsalvageable injuries in whom any therapy would be futile. When all patients were analyzed, rFVIIa had no statistical effect. When early deaths were excluded, rFVIIa reduced the need for blood transfusion in blunt trauma by 2.6 units ($P=0.02$) and massive transfusions ($P=0.03$), but not for penetrating trauma. There was no difference in harmful events, confirming its safety in trauma [18••]. Unpublished subgroup analysis corroborates the results of the 81-patient series described earlier in that among coagulopathic patients, rFVIIa is even more efficacious and reduces late complications like acute respiratory distress syndrome and mechanical ventilation days.

In spite of some limitations, this RCT remains the best available evidence in trauma, and supports the use of rFVIIa in blunt trauma, particularly if the patients are coagulopathic. Many issues remain for further study, including dosage (RCT 400 μg versus around 100 μg in most reports), timing of administration (after transfusion of 8 units and not as a last resort), cost/benefit and use in penetrating trauma and other subgroups.

Investigations in trauma are ongoing with a large (>1000 patients) phase III torso trauma RCT with patients about to start recruiting worldwide. There are also two ongoing RCTs on traumatic brain injury and one in burns. Trauma is possibly the surgical specialty most likely to be affected by rFVIIa. The results of further studies are anxiously awaited (Table 1) [19].

Cardiac surgery

Around the world, cardiac surgery is arguably the largest consumer of blood products. Perioperative bleeding is a major cause of morbidity and mortality, particularly in surgeries with cardiopulmonary bypass, accounting for the enormous interest and present widespread off-label use of rFVIIa [20].

Similar to other surgical specialties, many successful cases have been reported. In adults, Karkouti *et al.* [21] reported that the use of rFVIIa (35–70 μg/kg) in 51 cardiac surgery patients with refractory and massive postoperative bleeding reduced blood loss substantially. Except for increased renal dysfunction, adverse events were similar to matched control groups. Among pediatric patients, an open-label trial administered rFVIIa to eight children with postoperative bleeding refractory to conventional therapies, prior to reoperation. Either 30 or 60 μg/kg bolus was given initially and repeated up to four times. Re-operation was prevented in all but one patient, a remarkable result [22].

There is only one RCT in cardiac surgery by Diprose *et al.* [23••] suggesting that rFVIIa reduces blood transfusions in complex non-coronary cardiac surgery using cardiopulmonary bypass. This study unfortunately has shortcomings including being underpowered, restricting its application to support routine clinical use.

In spite of the lack of better evidence, the excellent results from case reports and series and the pathophysiology of perioperative bleeding seem to justify its off-label use in non-coronary cardiac surgery using cardiopulmonary bypass. In massively bleeding patients, doses between 35 and 80 μg/kg are suggested combined with intense efforts to correct coagulopathy and consideration for reoperation. Better studies are badly needed. There are at least two ongoing RCTs on rFVIIa salvage use in complex cardiac surgery (Table 1).

Liver surgery

Liver dysfunction is characterized by abnormal coagulation due to decreased synthesis of vitamin K-dependent factors, particularly factor VII, making rFVIIa an

Based on Mayer's results, rFVIIa is now an accepted therapy for ICH in North America. Evidence supporting other indications is virtually nonexistent but is changing with two ongoing RCTs in traumatic brain injury, three in ICH and one in re-bleeding after surgery for ICH (Table 1).

Perioperative use in urology, orthopedic and vascular surgery

There is not much experience reported on rFVIIa in these three areas. There are, however, well designed studies that deserve consideration. One of the strongest sources of evidence that rFVIIa might reduce perioperative blood loss was the RCT by Friederich *et al.* [31] in 36 patients undergoing elective retropubic prostatectomies. Patients receiving 20 or 40 μg/kg rFVIIa had a mean blood loss of 1235 and 1089 ml respectively, significantly lower than control 2688 ml ($P=0.001$). No patients on the higher dose required transfusion and adverse events were equally distributed. The benefits demonstrated are undeniable, however, because the bleeding reported in the control group is perceived as high, rFVIIa is not commonly used during elective prostatectomies. There is only one other study in urology, except for small case series of rFVIIa use in renal transplant bleeding [32–34].

There are few reports of rFVIIa use in orthopedics, with a single RCT published on the prophylactic perioperative use in reconstructive surgery for traumatic pelvic or acetabular fracture [35–37,38•]. This RCT concluded that 90 μg/kg of rFVIIa does not reduce perioperative blood loss, thus rFVIIa appears to have no role for this operation [38•]. In contrast, a European retrospective study [39] of 26 consecutive adolescents undergoing surgery for scoliosis demonstrated that a similar regimen of rFVIIa significantly reduced perioperative blood loss, need for transfusion and normalized the coagulation laboratory parameters. There is even less experience in vascular surgery. Manning *et al.* [40] reported eight patients with intraoperative or postoperative bleeding refractory to conventional measures treated with 40 μg/kg rFVIIa bolus; seven patients responded to rFVIIa.

The available evidence suggests that rFVIIa might reduce perioperative blood loss in some but not all operations, thus justifying both further investigation and the use of rFVIIa to treat occasional large perioperative bleedings.

Obstetric and gynecologic surgery

Obstetric and gynecologic surgery is another specialty familiar with massively bleeding patients. The potential benefit of rFVIIa is clear and interest easily understandable. Unfortunately to date the experience reported in this field is limited and consists exclusively of case reports, case series and abstracts presented in conferences. As in other areas, most reports describe positive results. RFVIIa has been used postpartum, after C-section and after pelvic surgery and other obstetric and gynecologic life-threatening bleedings [41–45].

Until better evidence is generated, rFVIIa use seems warranted for patients with intractable massive bleedings despite attempts to correct coagulopathy, thrombocytopenia and surgical intervention. Guidelines for use are cautiously recommended as similar to those in trauma and cardiac surgery. Considering the potential clinical effect, better studies in obstetric and gynecologic surgery are needed.

Adverse effects

RFVIIa is a novel drug in surgery and caution is recommended. The incidence of side effects in surgery is unknown but current evidence suggests that rFVIIa is safe. The most concerning complications are thromboembolic, including myocardial infarction, stroke, deep vein thrombosis and pulmonary embolus. After more than 10 years and over 700 000 doses, only 1% of the patients using rFVIIa for hemophilia developed such complications [46]. In patients without previous coagulopathy thromboembolic complications are described in 1–2%, but in patients with predisposing factors, such as those with ICH, adverse events reached 7% [47•]. Thus rFVIIa seems safe but not devoid of harmful effects [48,49•].

Conclusion

The ideal of stopping fatal bleeding anywhere in the body simply by administering an intravenous drug now seems possible, at least in some surgical conditions. The recent recognition of this potential has led to a widespread off-label use of rFVIIa in numerous bleeding conditions. Early successful reports encouraged further and more rigorous studies that now are starting to define the actual role of rFVIIa in surgery.

Some principles seem already well established. RFVIIa is an adjunct and not a substitute for current standards of care. It is indicated for both ICH and massive perioperative and traumatic bleeding that do not respond to attempts to correct hypothermia, coagulopathy, thrombocytopenia and surgical hemostasis, and should be reserved for salvageable patients.

Many issues need to be investigated much further including efficacy, populations likely to benefit, dosage, repeated infusions, safety, cost–benefit and others. Until further evidence is generated the bedside decision to administer rFVIIa to a patient with life-threatening hemorrhage remains a matter of surgical judgment.

Клиническое применение фактора VII «on label»

- 1. Заместительная терапия у пациентов с гемофилией (ингибиторная форма) и тромбоцитопатиями, в том числе если, им предстоит плановая или экстренная хирургическая операция.

Клиническое применение фактора VII «off-label»

- 1. Профилактика и терапия вторичных нарушений гемостаза при травме и операциях, осложненных массивной кровопотерей в:
- - кардиохирургии
- - акушерстве и гинекологии
- - детской хирургии
- - неонатологии
- - нейрохирургии

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Off-Label Use of Recombinant Factor VIIa in United States Hospitals: 2000–2008

Aaron C. Logan, MD, PhD[1], **Veronica Yank, MD**[2,3], and **Randall S. Stafford, MD, PhD**[4]
[1]Department of Medicine, Divisions of Hematology and Blood and Marrow Transplantation, Stanford University School of Medicine, Stanford, CA

Results—Between 2000 and 2008, off-label use of rFVIIa in hospitals increased more than 140-fold, such that in 2008, 97% (95% CI, 96% to 98%) of 18311 in-hospital uses were off-label. In contrast, in-hospital use for hemophilia increased less than 4-fold and accounted for 3% (95% CI, 1.9% to 3.5%) of use in 2008. Cardiovascular surgery (29%; 95% CI, 21% to 33%) and trauma (29%; 95% CI, 19% to 38%) and intracranial hemorrhage (11%; 95%CI, 7.7% to 14%) were the most common indications for rFVIIa use. Across all indications, in-hospital mortality was 27% (95% CI, 19% to 34%), and 43% (95% CI, 35% to 50%) of patients were discharged to home.

Limitations—Accuracy and completeness of the discharge diagnoses and patient medication records in the database sample cannot be verified.

Conclusion—Off-label use of rFVIIa in the hospital setting far exceeds use for approved indications. These patterns raise concern about the application of rFVIIa to conditions that lack strong supporting evidence.

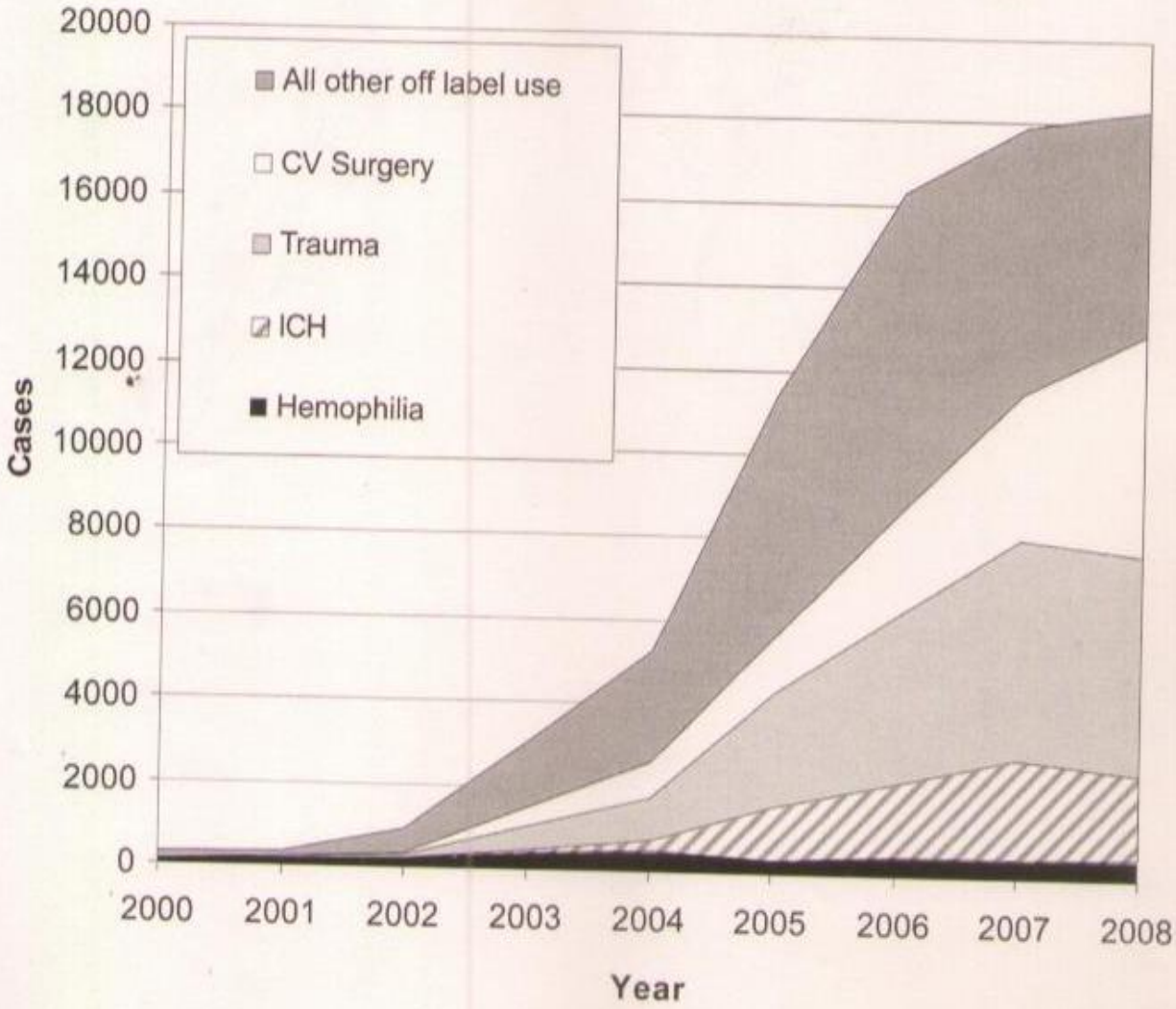

Figure 1.

Estimated Annual In-Hospital Cases* of rFVIIa Use for Hemophilia and Off-Label Indications.

* Cases signify the number of hospitalizations during which rFVIIa was used. The graph depicts all cases for each year. The width of each segment represents the number of cases for each category as indicated by differential shading. Hemophilia = Hemophilia A and B; ICH = Non-Traumatic Intracranial Hemorrhage; Trauma = Body and Brain Trauma; CV = Cardiovascular

Table 1

Indications for In-Hospital Use of Recombinant Factor VIIa.

Clinical Indication	Hospitalizations 2000–2008		Hospitalizations 2008 only	
	Estimated Cases	Percentage of Total	Estimated Cases	Percentage of Total
FDA approved indications				
Hemophilia A and B	3121	4.2	498	2.7
Off-label indications				
Adult cardiovascular surgery	12086	16.4	4862	26.6
Body trauma	11689	15.9	3214	17.6
Intracranial hemorrhage	7755	10.5	2005	11.0
Brain trauma	7158	9.7	2033	11.0
Primary clotting disorders	4104	5.6	792	4.3
Non-variceal GI bleeding	3881	5.3	713	3.9
Secondary clotting disorders	3744	5.1	766	4.2
Other liver disease	2451	3.3	539	2.9
Pediatric cardiovascular surgery	1684	2.3	387	2.1
Other vascular procedures	1515	2.0	381	2.1
Aortic aneurysm	1216	1.6	306	1.7
Pulmonary hemorrhage	1119	1.5	275	1.5
Cancer/stem cell transplant	1094	1.5	138	0.8
Variceal bleeding	897	1.2	235	1.3
Liver biopsy/resection	867	1.2	122	0.7
Neonatal indications	729	1.0	135	0.7
Obstetrical hemorrhage	672	0.9	220	1.2
Neurosurgery	500	0.7	108	0.6
Liver transplantation	132	0.2	58	0.3
Prostatectomy	120	0.2	0	0.0
Other procedures	3867	5.2	407	2.2
Other diagnoses	3345	4.5	117	0.6
Total treated with rFVIIa	73747	100	18311	100

Published in final edited form as:
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Comparative Effectiveness Review: Benefits and Harms of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications

Veronica Yank, M.D.[1,2,3], **C. Vaughan Tuohy, B.S.**[4], **Aaron C. Logan, M.D., Ph.D.**[5], **Dena M. Bravata, M.D., M.S.**[6,7], **Kristan Staudenmayer, M.D., M.S.**[8], **Robin Eisenhut, B.A.**[9], **Vandana Sundaram, M.P.H.**[6], **Donal McMahon, M.Sc., Ph.D.**[10], **Ingram Olkin, Ph.D.**[10], **Kathryn M. McDonald, M.M.**[6], **Douglas K. Owens, M.D., M.S.**[11,6], and **Randall S. Stafford, M.D., Ph.D.**[1,2]
[1]Program on Prevention Outcomes and Practices, Stanford Prevention Research Center, Stanford School of Medicine

Data Synthesis—Inclusion criteria were met by 17 RCTs, 33 comparative observational studies, and 23 non-comparative observational studies. Identified comparators were limited to placebo (RCTs) or usual care (observational studies). For intracerebral hemorrhage, mortality was not improved with FVIIa use across a range of rFVIIa doses. Arterial thromboembolism was increased with rFVIIa for medium-dose (risk difference 0.03 [0.01, 0.06]) and high-dose use (0.06 [0.01, 0.11]). For adult cardiac surgery, there was no mortality difference, but an increased risk of thromboembolism (0.05 [0.01, 0.10]) with rFVIIa. For body trauma, there were no differences in mortality or thromboembolism, but a reduced risk of acute respiratory distress syndrome (−0.05 [−0.02, −0.08]). Mortality and thromboembolism were consistently higher in observational studies compared to RCTs.

Limitations—The amount and strength of evidence was low for the majority of outcomes and indications. Publication bias could not be excluded.

Conclusion—Limited available evidence for five off-label indications indicates no mortality reduction with rFVIIa use. For some indications, rFVIIa increases thromboembolism.

Primary Funding Source—Agency for Healthcare Research and Quality

Клиническое применение фактора VII в нейрохирургии

- Все только «off label», за исключением плановых или экстренных нейрохирургических вмешательств у пациентов с гемофилией, тромбоцитопатиями и отсутствием VII фактора – крайне редкие ситуации.

Клиническое применение фактора VII в н/х

- 1. Черепно-мозговая травма, в особенности проникающая.
- 2. Хронические субдуральные гематомы.
- 3. Нейроонкологические вмешательства, осложненные массивной операционной кровопотерей у взрослых пациентов и детей.
- 4. Спинальные нейрохирургические вмешательства с массивной операционной кровопотерей.
- 5. Внутримозговые геморрагии.
- 6. Аневризматические САК.

Н/х вмешательства у больных с врожденными нарушениями гемостаза

- Это относительно редко встречаемые ситуации, приводимые в литературе как описания единичных клинических наблюдений.
- Проблем не возникает, если диагноз врожденной патологии гемостаза установлен до н/х операции. Использование концентрата недостающего фактора (в том числе препарата фактора rVIIa) в профилактическом или терапевтическом режиме, как правило, позволяет провести н/х вмешательство без каких либо осложнений.

British Journal of Anaesthesia 103 (6): 858–60 (2009)
doi:10.1093/bja/aep293 Advance Access publication October 20, 2009

BJA

Case Report

Recombinant activated factor VII for a patient with factor VII deficiency undergoing urgent intracerebral haematoma evacuation with underlying cavernous angioma

N. Liu[1], S. Aldea[2], D. François[3], M. Cherqui-Michel[1], M. Giansily-Blaizot[4] and M. Fischler[1]*

[1]Department of Anaesthesiology, [2]Department of Neurosurgery and [3]Department of Biology, Hôpital Foch, 40 rue Worth, 92151 Suresnes, France. [4]Department of Hemostasis, CHU Montpellier, France

47 летняя женщина, фактор VII 8%. Препарат во время и после операции.

Management of intracranial surgery for refractory epilepsy in severe factor VII deficiency: choosing the optimal dosing regimen

M. RAJPURKAR,* M. CALLAGHAN,* M. J. FREY,* K. SET,† H. CHUGANI† and S. SOOD‡

Division of Hematology Oncology, Carman and Ann Adams Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI, USA; †Division of Neurology, Carman and Ann Adams Department of Pediatrics, Children's Hospital of Michigan, Wayne State University, Detroit, MI, USA; and ‡Department of Neurosurgery Children's Hospital of Michigan, Detroit, MI, USA

8ми летний ребенок, генерализованные судороги в течение полугода по 20 приступов в день, фармакорезистентен. Каллозотомия. Препарат rVIIa до, во время и после хирургии.

A rare combination: congenital factor VII deficiency with Chiari malformation

Ali Bay[a], Elif Aktekin[b] and Ibrahim Erkutlu[c]

Congenital factor (VII) deficiency is a rare bleeding disorder. We present a patient with congenital FVII deficiency and congenital hydrocephalus who underwent a ventriculoperitoneal shunt operation and needed no prophylaxis after the procedure. *Blood Coagul Fibrinolysis* 26:946–948

Blood Coagulation and Fibrinolysis 2015, 26:946–948

Keywords: Chiari malformation, factor VII, hydrocephalus

[a]Department of Pediatrics, Division of Pediatric Hematology, [b]Department of Pediatrics and [c]Department of Neurosurgery, Gaziantep University, Gaziantep, Turkey

Correspondence to Ali Bay, Gaziantep Universitesi Tip Fakultesi Cocuk Hastaliklari Klinigi, Gaziantep 27310, Turkey
Tel: +90 342 3601200; fax: +90 342 3601013;
E-mail: abay1968@yahoo.com

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20 дневный ребенок, фактор VII 2%. Препарат до и во время операции.

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Published online 2016 May 6. doi: 10.1016/j.ijscr.2016.05.004

PMCID: PMC4885010

Elevated prothrombin time on routine preoperative laboratory results in a healthy infant undergoing craniosynostosis repair: Diagnosis and perioperative management of congenital factor VII deficiency

Kareen L. Jones,[a] Robert S. Greenberg,[a,b] Edward S. Ahn,[b,c] and Sapna R. Kudchadkar[a,b]

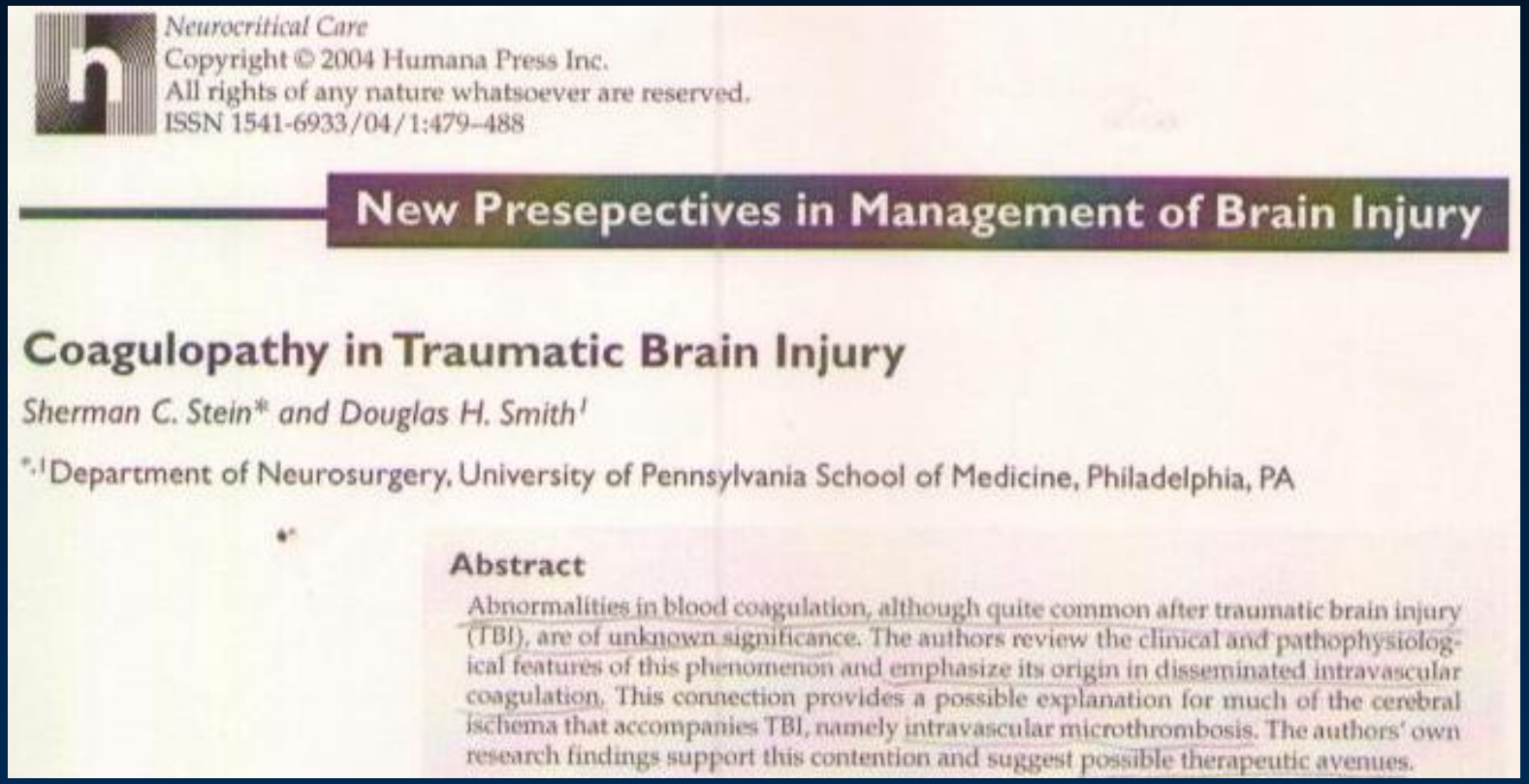
[a]Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University 1800 Orleans Street, Baltimore, MD 21287,United States
[b]Department of Pediatrics, The Johns Hopkins University, 1800 Orleans Street, Baltimore, MD 21287,United States
[c]Department of Neurosurgery, The Johns Hopkins University, 1800 Orleans Street, Baltimore, MD 21287, United States

2х месячный ребенок с краниостенозом. Препарат rVIIa до и во время операции.

Клиническое применение фактора VII в нейрохирургии - ЧМТ

- ЧМТ – самая частая н/х патология в России и в мире (в России 47 % от всей н/х патологии).
- Течение травматической болезни головного мозга сопровождается коагулопатией в 18 – 80 % случаев и она является вторичным фактором повреждения мозга.
- Механизмы : нарушение МК в зонах контузии и вторичная геморрагия в эти зоны.

ЧМТ



Neurocritical Care

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New Presepectives in Management of Brain Injury

Coagulopathy in Traumatic Brain Injury

Sherman C. Stein and Douglas H. Smith[1]*

*,[1]Department of Neurosurgery, University of Pennsylvania School of Medicine, Philadelphia, PA

Abstract

Abnormalities in blood coagulation, although quite common after traumatic brain injury (TBI), are of unknown significance. The authors review the clinical and pathophysiological features of this phenomenon and emphasize its origin in disseminated intravascular coagulation. This connection provides a possible explanation for much of the cerebral ischema that accompanies TBI, namely intravascular microthrombosis. The authors' own research findings support this contention and suggest possible therapeutic avenues.

- Коагулопатия при тяжелой ЧМТ является одним из вторичных факторов церебрального повреждения.

doi:10.1016/j.expneurol.2007.12.019.

Hemostatic and neuroprotective effects of human recombinant activated factor VII therapy after traumatic brain injury in pigs

Jun Zhang[a,f], Robert F. Groff IV[a], Xiao-Han Chen[a], Kevin D. Browne[a], Jason Huang[b], Eric D. Schwartz[c], David F. Meaney[d], Victoria E. Johnson[a], Sherman C. Stein[a], Rasmus Rojkjaer[e], and Douglas H. Smith[a,*]

[a] Department of Neurosurgery and Penn Center for Brain Injury and Repair, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

- Положительный эффект rVIIa был подтвержден в эксперименте на модели ЧМТ у свиней.

ЧМТ

Journal of Critical Care 30 (2015) 116–120

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Low-dose recombinant factor VIIa for reversing coagulopathy in patients with isolated traumatic brain injury

Qiang Yuan, MD [1], Xing Wu, MD [1], Zhuo-Ying Du, MD [1], Yi-Rui Sun, PhD, MD, Jian Yu, MD, Zhi-Qi Li, MD, Xue-Hai Wu, MD, Ying Mao, MD, Liang-Fu Zhou, MD, Jin Hu, MD *

Department of Neurosurgery, Huashan Hospital, Fudan University, Shanghai, People's Republic of China

ARTICLE INFO

Keywords:
Traumatic brain injury
Coagulopathy
Recombinant factor VIIa

ABSTRACT

Purpose: The purpose of this study was to investigate the role of low-dose recombinant factor VIIa (rFVIIa) (20 μg/kg) in reversing coagulopathy in patients with isolated traumatic brain injury (TBI).
Materials and methods: Patients with isolated TBI and coagulopathy at admission were enrolled prospectively from January 2010 to December 2011. The patients were divided into 2 groups: the rFVIIa and the no-rFVIIa

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Volume 2015, Article ID 261825, 10 pages
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Research Article

Coagulation Parameters and Risk of Progressive Hemorrhagic Injury after Traumatic Brain Injury: A Systematic Review and Meta-Analysis

Danfeng Zhang, Shun Gong, Hai Jin, Junyu Wang, Ping Sheng, Wei Zou, Yan Dong, and Lijun Hou

Department of Neurosurgery, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China

Correspondence should be addressed to Yan Dong; smmudongyan@163.com and Lijun Hou; lijunhoucz@126.com

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Черепно-мозговая травма

- У пострадавших с ЧМТ использование rVIIa, даже в небольших дозах (20 мкг/кг) давало положительный церебральный (уменьшение зоны поражения, геморрагического компонента, реже возникала потребность в н/х вмешательстве) и системный эффекты (статистически достоверно меньше частота РДСВ, длительности ИВЛ и исходы).

Особая ситуация – ЧМТ у пациентов на Варфарине

Acad Emerg Med. 2013 February ; 20(2): 140–145. doi:10.1111/acem.12074.

Risk of Traumatic Intracranial Hemorrhage in Patients with Head Injury and Preinjury Warfarin or Clopidogrel Use

Daniel K. Nishijima, MD, MAS, Steven R. Offerman, MD, Dustin W. Ballard, MD, David R. Vinson, MD, Uli K. Chettipally, MD, MPH, Adina S. Rauchwerger, MPH, Mary E. Reed, DrPH, James F. Holmes, MD, MPH, and for the Clinical Research in Emergency Services and Treatment (CREST) Network

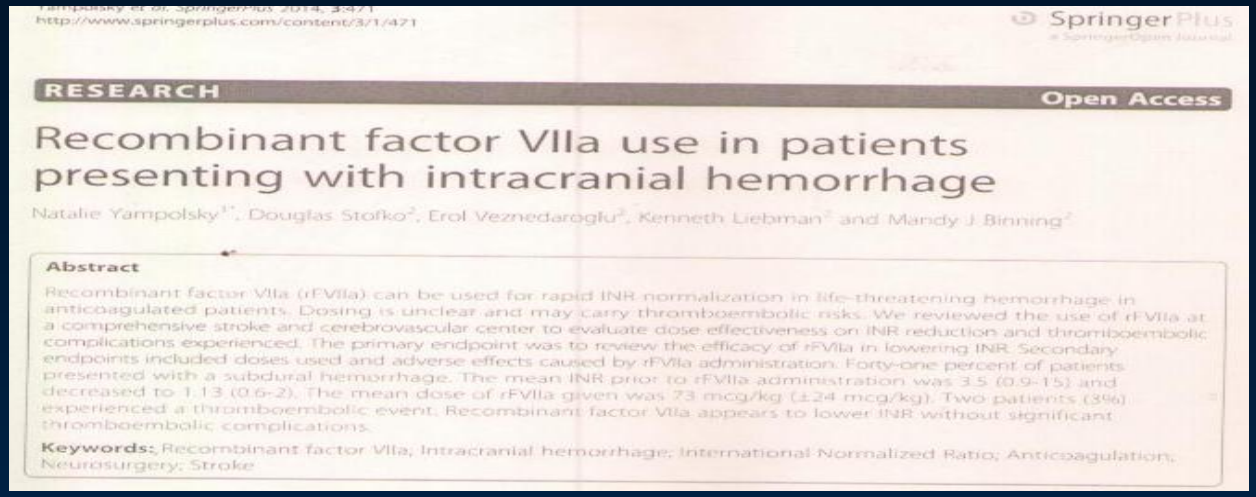
Department of Emergency Medicine, UC Davis School of Medicine, (DKN, JFH) Sacramento, CA; Kaiser Permanente South Sacramento Medical Center, (SRO) Sacramento, CA; Kaiser Permanente San Rafael Medical Center and Medical Offices, (DWB) San Rafael, CA; Kaiser Permanente Sacramento Medical Center and Medical Offices, (DRV) Sacramento, CA; Kaiser Permanente South San Francisco Medical Center and Medical Offices, (UKC) San Francisco, CA; Kaiser Permanente Division of Research, (ASR, MER) Oakland, CA

- Сравнение традиционного подхода (витамин К + СЗП + ингибиторы фибринолиза) с rVIIa, даже без традиционного лечения, показало преимущество фактора: достоверно более быстрая нормализация МНО и отсутствие вторичных осложнений (РДСВ).

Клиническое применение фактора VII в нейрохирургии – в/м геморрагии

- Спонтанные ВМК развиваются у 10 – 15 % населения (в Азии 20 – 30 %). Они сопровождаются примерно 50 % летальностью и высокой инвалидизацией (80 % в течении 6 месяцев). Н/х вмешательства по удалению гематом («большая» н/х) дали худшие результаты, поэтому таких больных лечат консервативно. Один из главных факторов ухудшения состояния у таких больных – увеличение объема гематомы. Причины спонтанных ВМК различны. Они могут развиваться на фоне интактного гемостаза (гипертонические, амилоидная ангиопатия и др.) и нарушенного (врожденно или антикоагулянтами – Варфарин).

ВМК



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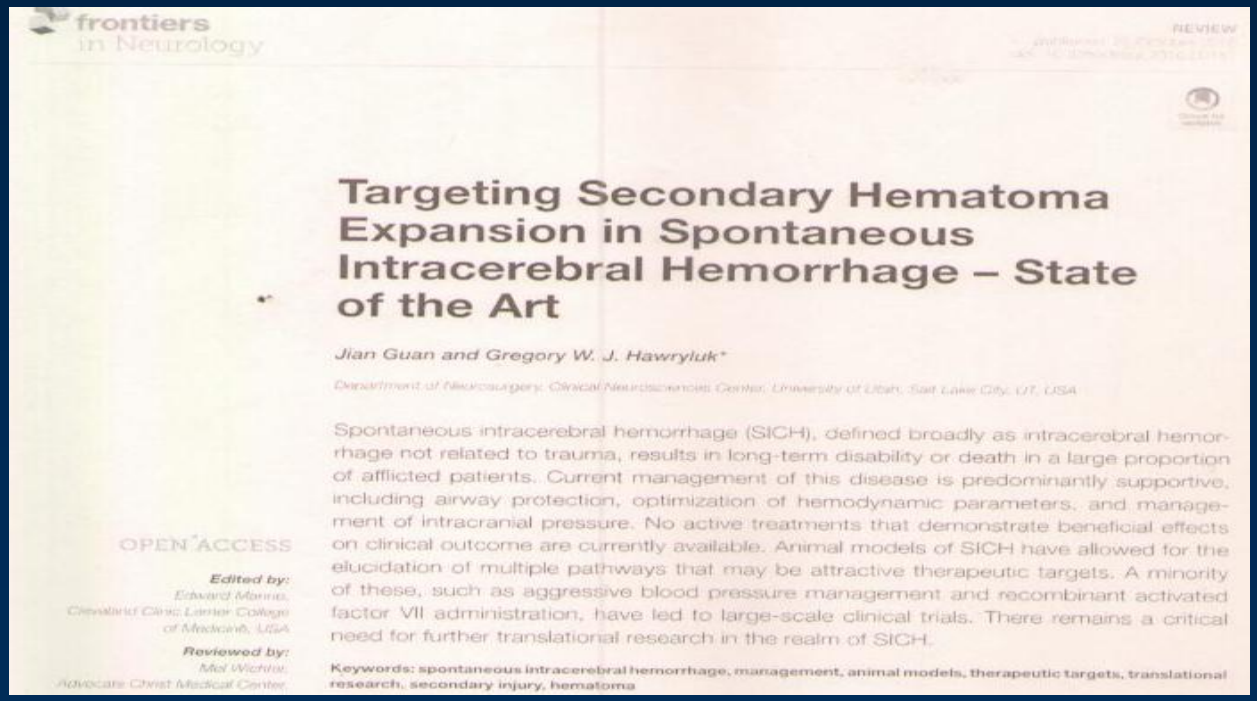
Recombinant factor VIIa use in patients presenting with intracranial hemorrhage

Natalie Yampolsky[1*], Douglas Stofko[2], Erol Veznedaroglu[3], Kenneth Liebman[3] and Mandy J Binning[3]

Abstract

Recombinant factor VIIa (rFVIIa) can be used for rapid INR normalization in life-threatening hemorrhage in anticoagulated patients. Dosing is unclear and may carry thromboembolic risks. We reviewed the use of rFVIIa at a comprehensive stroke and cerebrovascular center to evaluate dose effectiveness on INR reduction and thromboembolic complications experienced. The primary endpoint was to review the efficacy of rFVIIa in lowering INR. Secondary endpoints included doses used and adverse effects caused by rFVIIa administration. Forty-one percent of patients presented with a subdural hemorrhage. The mean INR prior to rFVIIa administration was 3.5 (0.9-15) and decreased to 1.13 (0.6-2). The mean dose of rFVIIa given was 73 mcg/kg (±24 mcg/kg). Two patients (3%) experienced a thromboembolic event. Recombinant factor VIIa appears to lower INR without significant thromboembolic complications.

Keywords: Recombinant factor VIIa; Intracranial hemorrhage; International Normalized Ratio; Anticoagulation; Neurosurgery; Stroke



frontiers in Neurology

REVIEW

Targeting Secondary Hematoma Expansion in Spontaneous Intracerebral Hemorrhage – State of the Art

*Jian Guan and Gregory W. J. Hawryluk**

Department of Neurosurgery, Clinical Neurosciences Center, University of Utah, Salt Lake City, UT, USA

Spontaneous intracerebral hemorrhage (SICH), defined broadly as intracerebral hemorrhage not related to trauma, results in long-term disability or death in a large proportion of afflicted patients. Current management of this disease is predominantly supportive, including airway protection, optimization of hemodynamic parameters, and management of intracranial pressure. No active treatments that demonstrate beneficial effects on clinical outcome are currently available. Animal models of SICH have allowed for the elucidation of multiple pathways that may be attractive therapeutic targets. A minority of these, such as aggressive blood pressure management and recombinant activated factor VII administration, have led to large-scale clinical trials. There remains a critical need for further translational research in the realm of SICH.

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Keywords: spontaneous intracerebral hemorrhage, management, animal models, therapeutic targets, translational research, secondary injury, hematoma

ВМК

Neurocrit Care. 2005 ; 2(3): 263–267. doi:10.1385/NCC:2:3:263.

Use of Recombinant Factor VIIa in Patients With Warfarin-Associated Intracranial Hemorrhage

David L. Brody, **Venkatesh Aiyagari**, **Angela M. Shackleford**, and **Michael N. Diringer***
Neurology/Neurosurgery Intensive Care Unit, Department of Neurology, Washington University School of Medicine, St. Louis, MO

Abstract

Introduction—Warfarin-associated intracranial hemorrhage (ICH) requires rapid normalization of clotting function. Current therapies are associated with significant complications and/or prolonged time to correction of coagulopathy. Recombinant factor VIIa (FVIIa) might allow faster and safer correction of coagulopathy.

Methods—This article presents a retrospective chart review of all patients with warfarin-associated ICH treated in a neurology/neurosurgery intensive care unit over an 11-month period.

Results—All patients were treated to rapidly reverse the warfarin effect. Fifteen patients received vitamin K and fresh frozen plasma (FFP) alone (FFP group). Twelve patients also received FVIIa (FVIIa group). The median times from presentation to an international normalization ratio (INR) of less than 1.3 were 32.2 and 8.8 hours in the FFP the FVIIa groups, respectively ($p = 0.016$). INR normalized slowly (at 110 and 130 hours, respectively) in two patients with end-stage renal failure who were given FVIIa, one of whom developed disseminated intravascular coagulation after three doses of FVIIa. No other complications occurred from FVIIa administration. One patient in the FFP group developed severe pulmonary edema.

Conclusion—FVIIa may be an effective adjunct to FFP in warfarin-related ICH, facilitating faster correction of INR and decreasing FFP requirements. A prospective, randomized trial is needed to confirm these preliminary findings and to determine whether there is a clinical benefit.

Keywords

Intracranial hemorrhage; warfarin; coagulopathy; fresh frozen plasma; factor VIIa

increases the plasma activities of factors IX and X in a dose-dependent manner (20). Observations of our patients and several previously published case series have demonstrated the efficacy of FVIIa in normalizing the INR as well as in stopping bleeding in a variety of clinical situations, including bleeding associated with excessive anticoagulation (9,11-13). Therefore, we believe that correction of the abnormal INR is likely to be associated with a correction of the in vivo coagulopathy as well.

Клиническое применение фактора VII в нейрохирургии – в/м геморрагии

- Раннее (до 4х ч после ВМК) введение препарата rVIIa уменьшает объем гематомы, предупреждает ее увеличение, иногда позволяет отказаться от н/х – по данным отдельных и серий наблюдений.
- RCT это подтвердили, но исходы в группах rVIIa и контрольной были одинаковы (!?!) и в группе rVIIa возросла частота артериальных тромбозов (7 – 13%).
- У больных с ВМК на фоне врожденных нарушений гемостаза препарат rVIIa его быстро нормализует.
- У больных в ВМК на фоне Варфарина препарат rVIIa позволяет быстро нормализовать МНО (менее 1,2) по сравнению с традиционной терапией (витамин К + СЗП + концентрат факторов).

BMK

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Review

A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia

Z.H. Yuan, J.K. Jiang, W.D. Huang *, J. Pan, J.Y. Zhu, J.Z. Wang

Department of Emergency, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310003, China

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ABSTRACT

Hematoma growth is common in intracerebral hemorrhage (ICH) and is associated with a poor outcome for patients. To evaluate the efficacy and safety of recombinant activated factor VII (rFVIIa) used as a hemostatic agent in patients with ICH without hemophilia, we searched Medline, Scopus, the Cochrane Library, Clinicaltrials.gov and the Stroke Trials Directory. Five randomized controlled trials were selected for analysis. Although rFVIIa can reduce the change in ICH volume, there was no significant difference in mortality, modified Rankin Scale (mRS) score or extended Glasgow Outcome Scale (GOS-E) score in patients treated with rFVIIa or placebo. There was a significant increase in arterial thromboembolic adverse events (TAE) in patients treated with rFVIIa. There was an increase in deep vein thrombosis in patients with spontaneous ICH and traumatic ICH. In conclusion, the use of rFVIIa reduces the growth of the hematoma but does not improve patient survival or functional outcome after ICH; in addition,

data may bias the analysis.

In conclusion, our meta-analysis suggests that rFVIIa reduces hematoma growth but does not improve survival or functional outcome after ICH. In addition, it increases the incidence of arterial TAE. However, it is still too early to judge the true efficacy of rFVIIa in the treatment of ICH, due to the limited trial data available. More large-scale clinical trials should be designed to carefully monitor the clinical benefit of rFVIIa in ICH, as well as thromboembolic risk.

ВМК

Can a Subset of Intracerebral Hemorrhage Patients Benefit From Hemostatic Therapy With Recombinant Activated Factor VII?

Stephan A. Mayer, MD; Stephen M. Davis, MD; Brett E. Skolnick, PhD; Nikolai C. Brun, MD, PhD; Kamilla Begtrup, MSc; Joseph P. Broderick, MD; Michael N. Diringer, MD; Thorsten Steiner, MD

Background and Purpose—In the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, 80 μg/kg of recombinant activated factor VII (rFVIIa) significantly reduced intracerebral hemorrhage (ICH) expansion when given within 4 hours of onset. However, in contrast to an earlier Phase 2b study, rFVIIa did not improve survival or functional outcome. In this exploratory analysis, we hypothesized that earlier treatment and exclusion of patients with a poor prognosis at baseline might enhance the benefit of rFVIIa treatment.

Methods—Using the FAST data set, the impact of rFVIIa (80 μg/kg) on poor outcome at 3 months (modified Rankin Score of 5 or 6) was systematically evaluated within subgroups using clinically meaningful cut points in onset-to-treatment time, age, and baseline ICH and intraventricular hemorrhage volume. The effect of treatment on outcome was analyzed using logistic regression, and ICH volume was analyzed with linear mixed models.

Results—A subgroup (n=160, 19% of the FAST population) was identified comprising patients ≤70 years with baseline ICH volume <60 mL, intraventricular hemorrhage volume <5 mL, and time from onset-to-treatment ≤2.5 hours. The adjusted ORs for poor outcome with rFVIIa treatment was 0.28 (95% CI, 0.08 to 1.06), whereas the reduction in ICH growth was almost doubled (7.3±3.2 versus 3.8±1.5 mL, $P=0.02$). The improved effect was confirmed in an analysis of similar Phase 2 patients.

Conclusions—A prospective trial would be needed to determine whether younger patients with ICH without extensive bleeding at baseline can benefit from 80 μg/kg of rFVIIa given within 2.5 hours of symptom onset. **(*Stroke*. 2009;40: 833-840.)**

- Повторный анализ больных исследования FAST (Factor Seven for Acute Hemorrhagic Stroke), но с исключением больных с заведомо плохим прогнозом. Положительный эффект от применения фактора оказался достоверным!

Клиническое применение фактора VII в нейрохирургии – аневризматические САК

- Pickard J.D., Kirkpatrick P.J., Melsen T., et al. «Potential role of NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage.// Blood Coag. Fibrinol. 2000 V. 11 Suppl. 1 p. S117-20.
- Применение rVIIa для профилактики рецидива аневризматического САК.
- 15 больных в остром периоде САК, НовоСевен по схеме 80 мкг/кг в/в с последующей инфузией 3,5 мкг/кг час.
- Исследование прекращено досрочно из-за тромботического осложнения (тромбоз ветвей СМА на контролатеральной аневризме стороне).

Клиническое применение фактора VII в нейрохирургии - нейроонкология

J Neurosurg 96:946–948, 2002

Application of recombinant activated factor VII during surgery for a giant skull base hemangiopericytoma to achieve safe hemostasis

Case report

RÜDIGER GERLACH, M.D., GERHARD MARQUARDT, M.D., HEIMO WISSING, M.D., INGE SCHARRER, M.D., PH.D., ANDREAS RAABE, M.D., AND VOLKER SEIFERT, M.D., PH.D.

Departments of Neurosurgery, Anesthesiology, and Medicine, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

The authors report on a 64-year-old woman with a huge recurrent skull base hemangiopericytoma, in whom they encountered severe difficulty in attaining intraoperative hemostasis. Standard surgical hemostatic methods and the administration of fresh-frozen plasma and prothrombin complex concentrates failed to stop diffuse bleeding from an inoperable tumor remnant. At a critical point during the operation, the intravenous administration of recombinant activated factor VII, combined with mechanical compression, finally led to satisfactory hemostasis. The rationale for using recombinant activated factor VII in situations of uncontrolled bleeding during neurosurgical procedures is discussed, along with the literature in which the use of recombinant activated factor VII as a maneuver of last resort is reported for hemostasis in other surgical fields.

KEY WORDS • factor VII • recombinant activated factor VII • hemostasis • coagulation

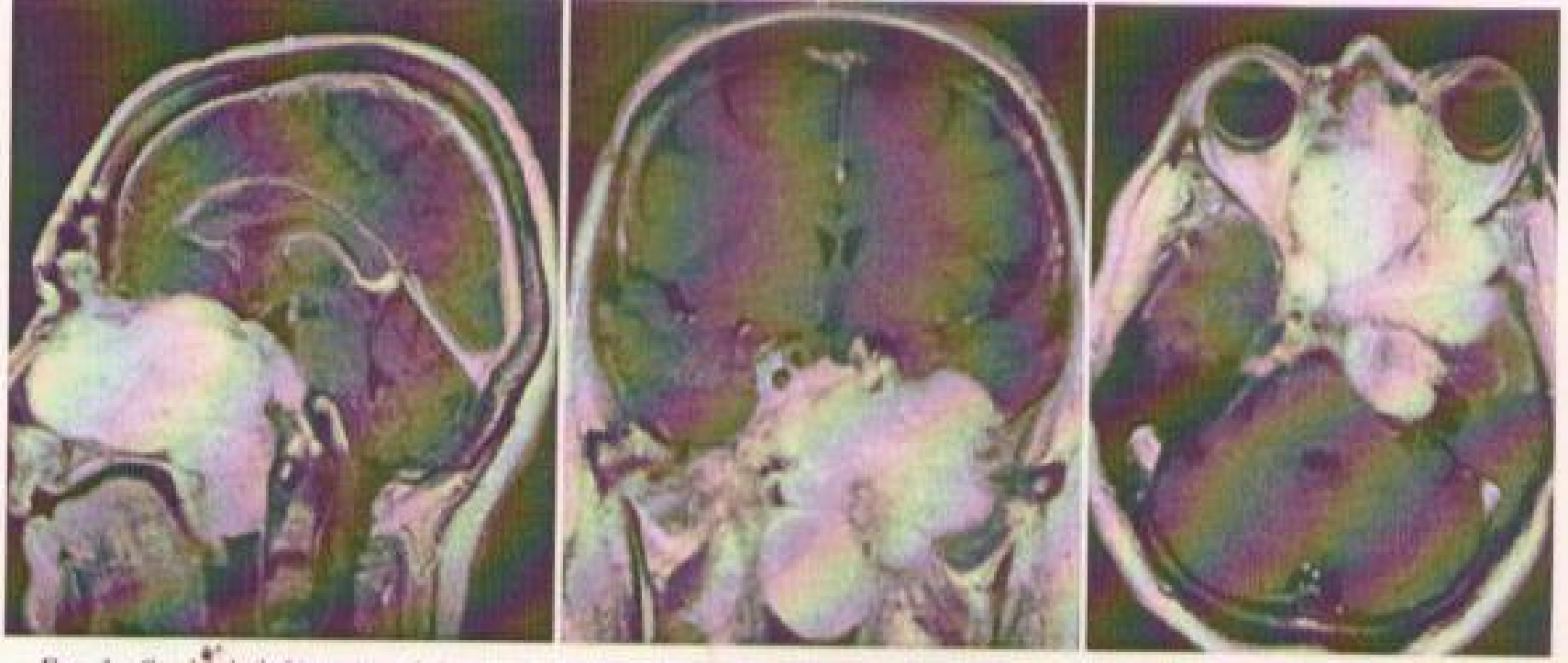


FIG. 1. Sagittal *(left)*, coronal *(center)*, and axial *(right)* contrast-enhanced cranial MR images demonstrating diffuse infiltration of the nasal septum, the orbital plate of ethmoid bone, the ethmoid and sphenoid sinus, with further extension toward the left temporal fossa and the clivus, and enclosing the left internal carotid artery.

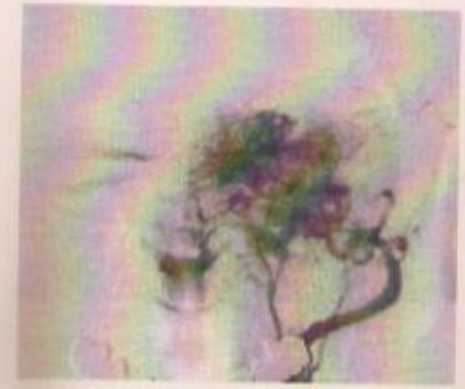
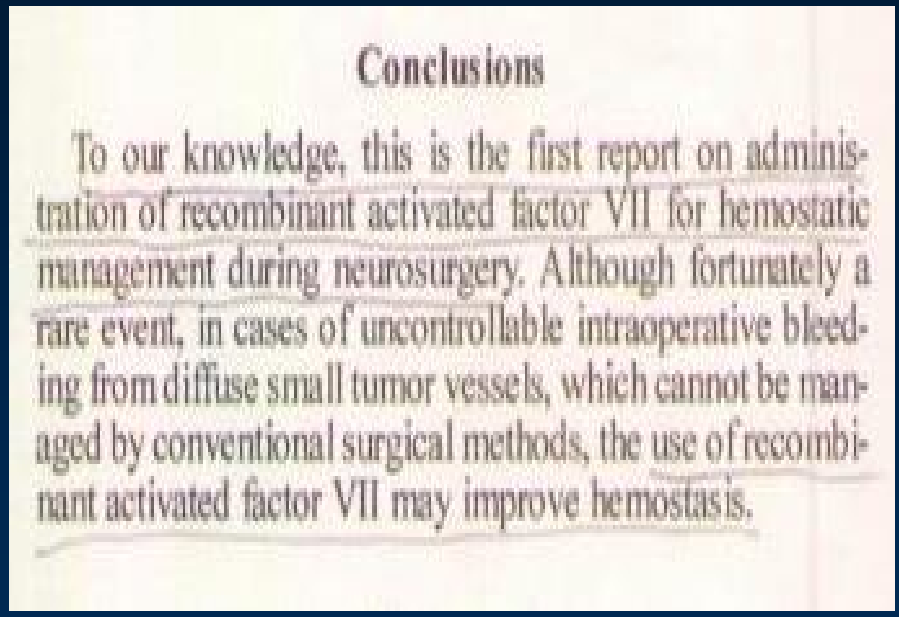


FIG. 2. Preoperative angiogram, anteroposterior view, revealing abundant tumor vascularization and typical corkscrew-shaped feeding arteries.

- Суммарный объем операционной кровопотери авторы не приводят, но для ее компенсации были использованы 39 доз донорской эритромассы, 29 доз концентраца тромбоцитов и 29 доз СЗП, а так же 5000 единиц антитромбина и 2400 единиц концентрата протромбинового комплекса!!!
- При неэффективности всего этого было введено 2 Х 9,6 мг rVIIa (120 мкг/кг) с интервалом в 2 часа. Адекватный гемостаз удалось достичь через 10 минут после в/в введения первой дозы фактора.



Conclusions

To our knowledge, this is the first report on administration of recombinant activated factor VII for hemostatic management during neurosurgery. Although fortunately a rare event, in cases of uncontrollable intraoperative bleeding from diffuse small tumor vessels, which cannot be managed by conventional surgical methods, the use of recombinant activated factor VII may improve hemostasis.

J Neurosurg 98:737–740, 2003

The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings

JULIAN LIN, M.D., WILLIAM C. HANIGAN, M.D., PH.D., MICHAEL TARANTINO, M.D., AND JOHN WANG, M.D.

Department of Neurological Surgery and Pediatrics, University of Illinois College of Medicine at Peoria, Illinois

Object. In this report the authors describe the use of the hemostatic agent recombinant activated factor VII (rFVIIa) in the perioperative treatment of hemorrhages in the central nervous system that are associated with warfarin therapy.

Methods. Two patients sustained hemorrhages within the spinal canal, and the other two had acute intracranial subdural hematomas. All patients had normal platelet counts, activated partial thromboplastin times, and fibrinogen levels, and all received fresh frozen plasma in conjunction with rFVIIa. The initial international normalized ratios (INRs) ranged from 1.9 to 5.6. Each dose of rFVIIa was 1200 μg, ranging from 16 to 22 μg/kg of body weight. Two patients received two perioperative doses of rFVIIa; the others required just one dose before surgery. The INR normalized within 2 hours of administration of rFVIIa in all patients. There were no thromboembolic complications, and surgical blood loss was less than 100 ml for all operations.

Conclusions. This clinical experience indicates that rFVIIa may be safe and effective as the initial hemostatic agent for rapid reversal of orally administered anticoagulation medications in patients who require urgent neurosurgical intervention.

KEY WORDS • intracranial hemorrhage • warfarin sodium • recombinant activated factor VII

- 4 больных, 2 со спинальными и 2 с субдуральными гематомами на фоне Варфарина. После rVIIa отмечена быстрая нормализация МНО. Нх вмешательства кровопотерей не сопровождались.

TABLE 1

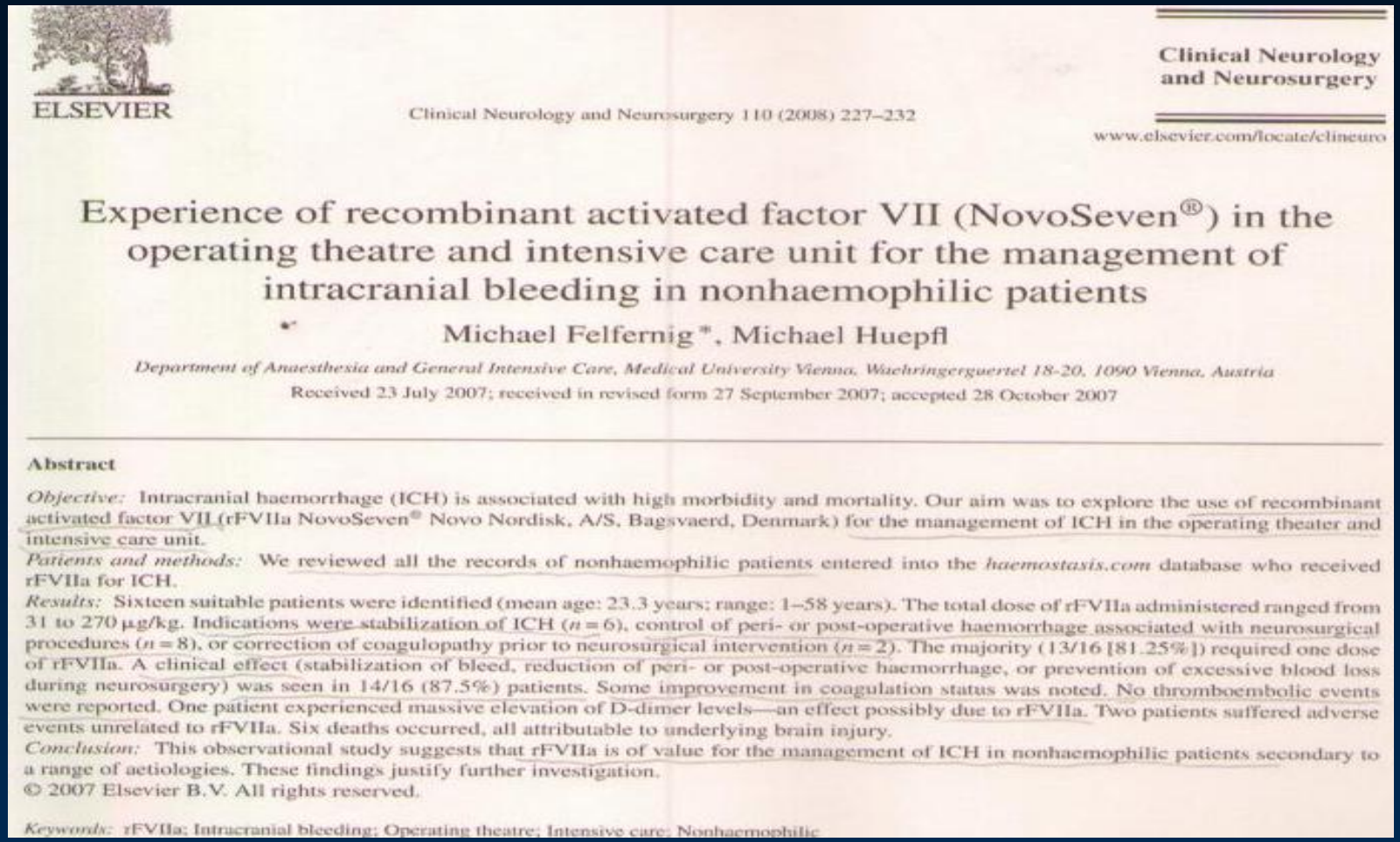
*Clinical characteristics, treatments, and outcomes in four consecutive patients with CNS hemorrhages associated with warfarin anticoagulation**

Case No.	Age (yrs), Sex	Preexisting Condition	Diagnosis	Time to Op†	Initial INR	Tx Before or During Op	INR After Initial Tx	Postop Tx (hrs)	Outcome (mos)
1	64, F	artificial heart valve, atrial fibrillation, CHF, DVT	acute cervical EDH, C3–6	6 hrs	5.6	2 U FFP, 1200 μg rFVIIa preop	1.0 preop	2 U FFP + 1200 μg rFVIIa (24)	death (1.5)
2	68, F	DVT	acute lumbar SDH, L1–3	8.5 hrs	2.9	1200 μg rFVIIa preop, followed by 1 U FFP	1.0 immed preop	2 U FFP + 1200 μg rFVIIa (27)	good (5)
3	66, M	chronic ethanolism, DVT	acute cortical SDH	45 mins	1.9	1200 μg rFVIIa, followed by 2 U FFP during op	1.0 at end of op	none	excellent (3)
4	53, M	headache, confusion, CLL, DVT	acute cortical SDH	17 hrs	2.8	5 U FFP preop, followed by 1200 μg rFVIIa immed preop	2.8, reduced to 1.7 immed preop; reduced to 0.8 during op	1 U FFP (12)	excellent (2)

* CHF = congestive heart failure; CLL = chronic lymphocytic leukemia; EDH = epidural hematoma; immed = immediately; Tx = treatment.
† Time elapsed between neurosurgical consultation and surgery.

Conclusions

The clinical and laboratory outcomes for this small series indicate that rFVIIa may be used as an initial hemostatic agent for the rapid reversal of warfarin-induced anticoagulation. With one to two preoperative doses (each dose consisting of one 1200-μg vial of rFVIIa) combined with FFP, patients attained normalization of the INR before or during surgery. The duration of the reversal or the necessity for multiple postoperative doses cannot be determined based on this study. Nevertheless, rFVIIa may be a safe and effective, rapid-acting hemostatic agent for reversal of warfarin-induced anticoagulation in patients with hemorrhages in the CNS who require surgical intervention. The higher cost and need for multiple doses may limit the use of rFVIIa for routine reversal of warfarin therapy in patients who do not require surgical intervention. Finally, the usefulness of rFVIIa in patients with hemorrhages in the CNS that are associated with other abnormalities in the clotting mechanism cannot be determined from this series.



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Experience of recombinant activated factor VII (NovoSeven®) in the operating theatre and intensive care unit for the management of intracranial bleeding in nonhaemophilic patients

Michael Felfernig *, Michael Huepfl

Department of Anaesthesia and General Intensive Care, Medical University Vienna, Waehringerguertel 18-20, 1090 Vienna, Austria

Received 23 July 2007; received in revised form 27 September 2007; accepted 28 October 2007

Abstract

Objective: Intracranial haemorrhage (ICH) is associated with high morbidity and mortality. Our aim was to explore the use of recombinant activated factor VII (rFVIIa NovoSeven® Novo Nordisk, A/S, Bagsvaerd, Denmark) for the management of ICH in the operating theater and intensive care unit.

Patients and methods: We reviewed all the records of nonhaemophilic patients entered into the *haemostasis.com* database who received rFVIIa for ICH.

Results: Sixteen suitable patients were identified (mean age: 23.3 years; range: 1–58 years). The total dose of rFVIIa administered ranged from 31 to 270 μg/kg. Indications were stabilization of ICH ($n = 6$), control of peri- or post-operative haemorrhage associated with neurosurgical procedures ($n = 8$), or correction of coagulopathy prior to neurosurgical intervention ($n = 2$). The majority (13/16 [81.25%]) required one dose of rFVIIa. A clinical effect (stabilization of bleed, reduction of peri- or post-operative haemorrhage, or prevention of excessive blood loss during neurosurgery) was seen in 14/16 (87.5%) patients. Some improvement in coagulation status was noted. No thromboembolic events were reported. One patient experienced massive elevation of D-dimer levels—an effect possibly due to rFVIIa. Two patients suffered adverse events unrelated to rFVIIa. Six deaths occurred, all attributable to underlying brain injury.

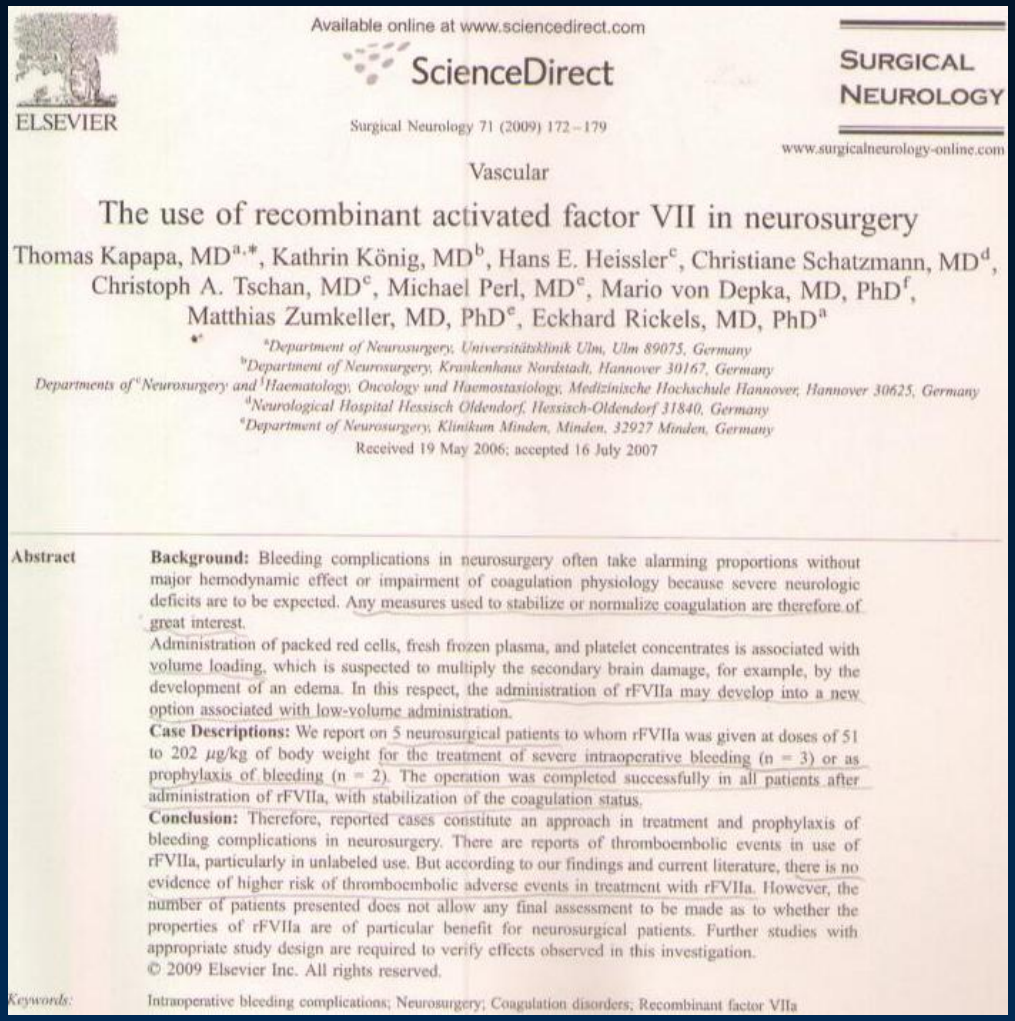
Conclusion: This observational study suggests that rFVIIa is of value for the management of ICH in nonhaemophilic patients secondary to a range of aetiologies. These findings justify further investigation.

Keywords: rFVIIa; Intracranial bleeding; Operating theatre; Intensive care; Nonhaemophilic

- 16 нх больных с интракраниальными геморрагиями, у которых фактор был использован до, во время или после операции. Хороший эффект во всех наблюдениях.

a risk/benefit analysis should be carried out in all patients before administration of rFVIIa.

Observational studies that use data collected from global registries have several limitations, including heterogeneous patient populations, incomplete and subjective data, use of different treatment practices, logistical difficulties in retrieving data, and limitation of data to cases for which clinician approval has been received. Nonetheless, this study suggests that administration of rFVIIa is a promising treatment for intracranial bleeds across a range of indications and correction of coagulopathy prior to neurosurgery. Importantly, no thromboembolic events were observed, although the elevation of D-dimer levels in one patient highlights the importance of further investigation of the agent in this indication.



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Vascular

The use of recombinant activated factor VII in neurosurgery

Thomas Kapapa, MD[a,*], Kathrin König, MD[b], Hans E. Heissler[c], Christiane Schatzmann, MD[d], Christoph A. Tschan, MD[c], Michael Perl, MD[e], Mario von Depka, MD, PhD[f], Matthias Zumkeller, MD, PhD[e], Eckhard Rickels, MD, PhD[a]

[a]Department of Neurosurgery, Universitätsklinik Ulm, Ulm 89075, Germany
[b]Department of Neurosurgery, Krankenhaus Nordstadt, Hannover 30167, Germany
Departments of [c]Neurosurgery and [f]Haematology, Oncology und Haemostasiology, Medizinische Hochschule Hannover, Hannover 30625, Germany
[d]Neurological Hospital Hessisch Oldendorf, Hessisch-Oldendorf 31840, Germany
[e]Department of Neurosurgery, Klinikum Minden, Minden, 32927 Minden, Germany

Received 19 May 2006; accepted 16 July 2007

Abstract

Background: Bleeding complications in neurosurgery often take alarming proportions without major hemodynamic effect or impairment of coagulation physiology because severe neurologic deficits are to be expected. Any measures used to stabilize or normalize coagulation are therefore of great interest.

Administration of packed red cells, fresh frozen plasma, and platelet concentrates is associated with volume loading, which is suspected to multiply the secondary brain damage, for example, by the development of an edema. In this respect, the administration of rFVIIa may develop into a new option associated with low-volume administration.

Case Descriptions: We report on 5 neurosurgical patients to whom rFVIIa was given at doses of 51 to 202 μg/kg of body weight for the treatment of severe intraoperative bleeding (n = 3) or as prophylaxis of bleeding (n = 2). The operation was completed successfully in all patients after administration of rFVIIa, with stabilization of the coagulation status.

Conclusion: Therefore, reported cases constitute an approach in treatment and prophylaxis of bleeding complications in neurosurgery. There are reports of thromboembolic events in use of rFVIIa, particularly in unlabeled use. But according to our findings and current literature, there is no evidence of higher risk of thromboembolic adverse events in treatment with rFVIIa. However, the number of patients presented does not allow any final assessment to be made as to whether the properties of rFVIIa are of particular benefit for neurosurgical patients. Further studies with appropriate study design are required to verify effects observed in this investigation.

Keywords: Intraoperative bleeding complications; Neurosurgery; Coagulation disorders; Recombinant factor VIIa

- 5 нх больных, у которых фактор был применен для лечения или профилактики массивной кровопотери. Эффект достигнут во всех наблюдениях.

Table 1
Summary of cases

Case	Age, sex	Bleeding situation	Measures taken before rFVIIa	rFVIIa dose	Hemostasis	Neurologic outcome
1	28, f	Diffuse intraoperative bleeding during surgery of cerebral arteriovenous malformation	30 PRC, 24 FFP, 2 PC	94 μg/kg	Yes	Hemiparesis
2	23, f	Massive intraoperative bleeding from venous bony canals during OP of a metastasis of the cranial vault/intradural	40 PRC, 28 FFP, 2 PC	202 μg/kg	Yes	OPS
3	66, f	Uncontrollable bleeding in the presence of FVII deficiency and OP of a thoracic vertebra 10 mass with medullary compression	24 PRC, 12 FFP, 3 PC, 2000 kIU prothrombin complex	88 μg/kg	Yes	No deficit except an impairment of sensation along the approach
4	81, m	Pre-OP prophylaxis of bleeding in patient with spinal canal stenosis with tetraparesis and multiple coagulopathy, essential thrombocytopenia, Glanzmann-like platelet defect, factor V deficiency, von Willebrand disease type IIa	Haemate (approximately 3000 kIU/d)	89 μg/kg	No increased bleeding tendency	Marked regression of tetraparesis
5	44, m	Pre-OP prophylaxis of bleeding in patient with cranial and intracerebral stab wound	None	51 μg/kg	No bleeding complication	Anisocoria and hemiparesis with post-OP improvement

PRC indicates packed red cells; FFP, fresh frozen plasma; OP, operation; OPS, organic psychosyndrome; PC, platelet concentrate.

5. Conclusion

In neurosurgical operations in which no adequate blood coagulation can be maintained owing to the duration of the operation or the extended operative field, a status of coagulation with better hemostasis could be obtained by the use of rFVIIa. Because the coagulation parameters remained within physiologic reference ranges on further monitoring after the administration of rFVIIa, a short-term postoperative reduction of the risk of postoperative bleeding after mass transfusion is possible, too. It seems that the coagulation-improving effect in surgical situations occurs in various coagulation disorders such as factor V deficiency or FVII deficiency. No thromboembolic complications occurred after administration of rFVIIa in the cases presented.

In neurosurgery, a surgical discipline with limited possibility of mechanic control of bleeding, rFVIIa represents an option to stabilize and normalize coagulation, although data is still limited. The positive experiences should encourage further studies with a larger sample size.

Recombinant activated factor VII for a warfarinised Jehovah's Witness with an acute subdural haematoma

Rimma Goldberg [a], Katharine J. Drummond [a,b,*]

[a] Department of Neurosurgery, The Royal Melbourne Hospital, Parkville, Victoria 3050, Australia
[b] Department of Surgery, The University of Melbourne, Parkville, Victoria, Australia

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Abstract

Recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) is a haemostatic agent first developed for bleeding associated with haemophilia and trauma, but for which the indications continue to expand. Recent reports have suggested efficacy for various types of intracranial haemorrhage and for patients with abnormalities of coagulation. We report a warfarin-anticoagulated Jehovah's Witness patient with an acute subdural haematoma for whom rFVIIa was used perioperatively. The haematoma was surgically evacuated without excessive blood loss and the patient eventually made a good recovery, returning to independent self-care.

Keywords: Recombinant activated factor VIII; Acute subdural haematoma; Surgery; Anticoagulation; Warfarin; Jehovah's Witness

Fig. 2. Axial CT scan 2 days postoperative, showing a recollection of the haematoma in the extra- and subdural spaces. Despite the large haematoma, there is less midline shift and compression of the ventricles due to the craniectomy

Клиническое применение фактора VII в нейрохирургии – спинальная н/х

SYSTEMATIC REVIEW ARTICLE

Spine Surgery and Blood Loss: Systematic Review of Clinical Evidence

Dafna Willner, MD,* Valeria Spennati, MD,† Shelly Stohl, MD,* Giulia Tosti, MD,† Simone Aloisio, MD,† Federico Bilotta, MD, PhD†

Spine surgery has been growing rapidly as a neurosurgical operation, with an increase of 220% over a 15-year period. Intraoperative blood transfusion is a major outcome determinant of spine procedures. Various approaches, including pharmacologic and nonpharmacologic therapies, have been tested to decrease both intraoperative and postoperative blood loss. The aim of this systematic review is to report clinical evidence on the relationship between intraoperative blood loss (primary outcome) and on transfusion requirements and postoperative complications (secondary outcomes) in patients undergoing spine surgery. A literature search of PubMed database was performed using 5 key words: spine surgery and transfusion; spine surgery and blood loss; spine surgery and blood complications; spine surgery and deep vein thrombosis; and spine surgery and pulmonary embolism. Clinical reports (randomized controlled trials, prospective and retrospective studies, and case reports) were selected. A total of 473 articles were examined; 450 were excluded, and 24 were selected for this systematic review. Selected articles were categorized into 3 subchapters: (1) drugs active on coagulation (12 studies): tranexamic acid, aminocaproic acid, aprotinin, and recombinant activated factor VII; (2) drugs not active on coagulation (5 studies): ketorolac, epoetin alfa, magnesium sulfate, propofol/sevoflurane, and omega-3 and fish oil; (3) nonpharmacologic approaches (7 studies): surgical tips, patient positioning, and general or spinal anesthesia. Several studies have shown a significant reduction in intraoperative bleeding during spine surgery and in the requirement for blood transfusion. (Anesth Analg 2016;123:00–00)

Клиническое применение фактора VII в нейрохирургии – спинальная н/х

Eur Spine J (2004) 13 (Suppl. 1): S83–S88
DOI 10.1007/s00586-004-0736-y

REVIEW

Richard B. Weiskopf

The use of recombinant activated coagulation factor VII for spine surgery

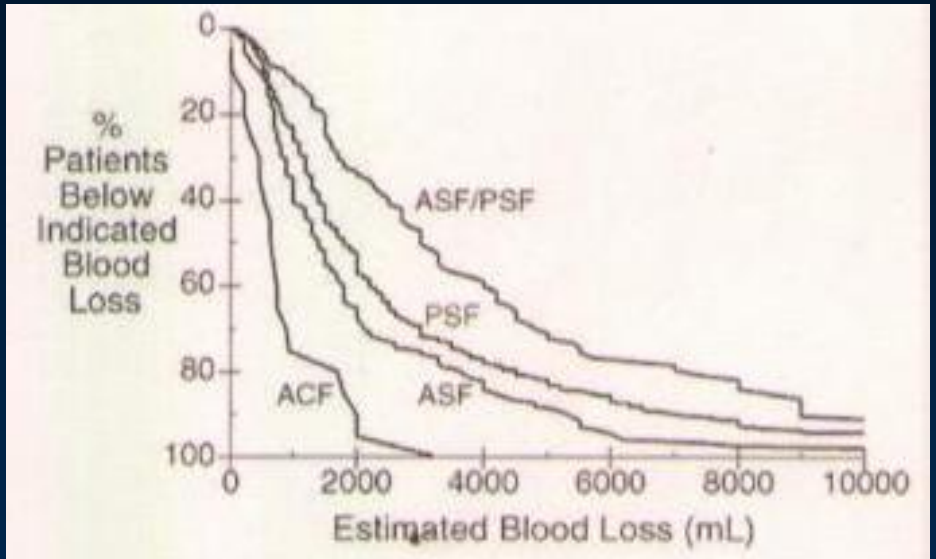


Fig. 1 Estimated blood loss in spinal surgery of 1,003 patients (March 2000–May 2003) for whom intra-operative cell salvage was used. Data for each procedure (*ACF* anterior cervical fusion; *ASF* anterior spinal (thoracic and/or lumbar) fusion; *PSF* posterior spinal (thoracic and/or lumbar) fusion; *ASF/PSF* anterior/posterior spinal fusion) show the cumulative number of patients who had that amount or less of blood loss. Data collected and analyzed with institutional review board approval (Committee on Human Research, University of California, San Francisco, CA, USA)

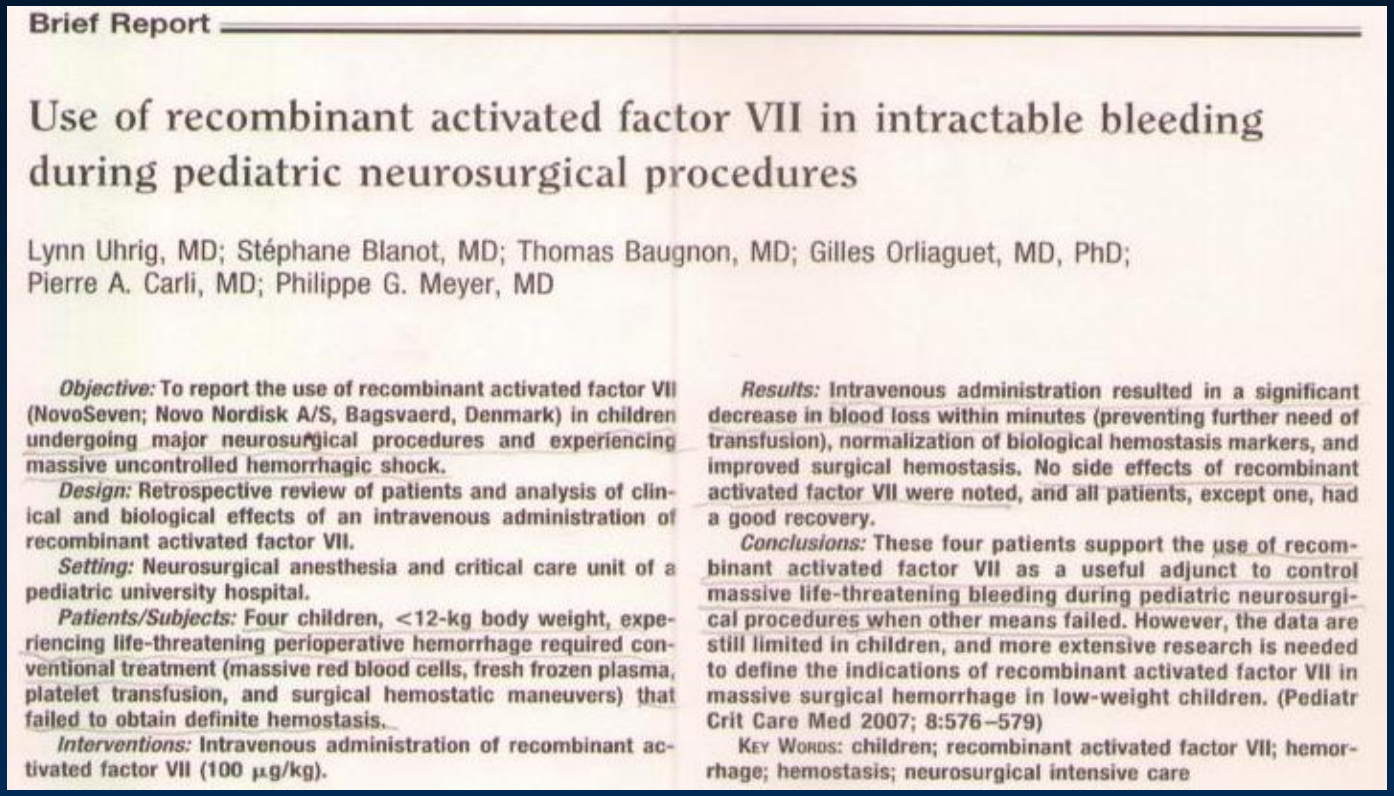
DVT (NAF group) and a PE (TXA group). Because of the nature of the study, the authors were unable to accurately assess dosing information, making these results somewhat problematic.

Recombinant Activated Factor VII. The role of rFVIIa in reducing perioperative blood loss was assessed in 1 randomized study.[23] A total of 36 patients were randomly assigned to receive rFVIIa in 3 different doses (12 patients per dose). The rFVIIa doses were 30 μg/kg rFVIIa, 60 μg/kg rFVIIa, and 120 μg/kg rFVIIa. An additional 13 patients received placebo. The dosing trigger was a 10% loss of estimated blood volume during surgery. When the dosing trigger was reached, each randomized patient received a total of 3 identical doses of rFVIIa or placebo (when the trigger was reached and again at 2 and 4 hours after the initial dose). Treatment with rFVIIa significantly decreased the adjusted mean volume of blood loss during surgery, compared with the placebo, by 56%, 84%, and 68% for the 30, 60, and 120 μg/kg rFVII groups, respectively ($P < .001$). In addition, rFVIIa significantly decreased the adjusted mean transfusion volumes during surgery, as compared with placebo, by 83% (30 μg/kg; $P < .002$), 95% (60 μg/kg; $P < .001$), and 81% (120 μg/kg; $P < .001$). Recombinant FVIIa reduced the number of units of allogeneic blood products transfused (5 in placebo-treated group as compared with 1.1, 1.3, and 1.8 in the 30, 60, and 120 μg/kg rFVIIa groups, respectively; $P = .03$ for each dose, as compared with placebo). There were 8 serious adverse events; 2 in the placebo group, 3 in the 30 μg/kg rFVIIa group, and 3 in the 60 μg/kg rFVIIa group, of which 1 was fatal. No serious adverse events were observed in the 120 μg/kg rFVII group. In the 30 μg/kg rFVIIa group, there was 1 fatal thromboembolic stroke and 1 myocardial infarction. The majority of other potentially thrombotic events increased in troponin I levels (and 1 event of reduced visual acuity in the placebo group).

Клиническое применение фактора VII в нейрохирургии – спинальная н/х

In summary, rFVIIa appears likely to be efficacious in states of decreased concentration of coagulation factors, thrombocytopenia, and in at least some states of altered platelet function. While efficacy has been found in one small study, it has not been demonstrated in large, randomized, double-blinded, placebo-controlled trials published in the peer-reviewed literature. Many clinicians now use rFVIIa to treat intra-operative hemorrhages not easily controlled by conventional therapy. A trial of substantial size in spinal surgery may be undertaken in the near future. Until adequate data demonstrating safety and efficacy are fully reported, it would seem appropriate to reserve the use of rFVIIa in spinal surgery to those cases where conventional therapy cannot provide adequate hemostasis.

Клиническое применение фактора VII в н/х – детская нейроонкология



Brief Report

Use of recombinant activated factor VII in intractable bleeding during pediatric neurosurgical procedures

Lynn Uhrig, MD; Stéphane Blanot, MD; Thomas Baugnon, MD; Gilles Orliaguet, MD, PhD; Pierre A. Carli, MD; Philippe G. Meyer, MD

Objective: To report the use of recombinant activated factor VII (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) in children undergoing major neurosurgical procedures and experiencing massive uncontrolled hemorrhagic shock.

Design: Retrospective review of patients and analysis of clinical and biological effects of an intravenous administration of recombinant activated factor VII.

Setting: Neurosurgical anesthesia and critical care unit of a pediatric university hospital.

Patients/Subjects: Four children, <12-kg body weight, experiencing life-threatening perioperative hemorrhage required conventional treatment (massive red blood cells, fresh frozen plasma, platelet transfusion, and surgical hemostatic maneuvers) that failed to obtain definite hemostasis.

Interventions: Intravenous administration of recombinant activated factor VII (100 μg/kg).

Results: Intravenous administration resulted in a significant decrease in blood loss within minutes (preventing further need of transfusion), normalization of biological hemostasis markers, and improved surgical hemostasis. No side effects of recombinant activated factor VII were noted, and all patients, except one, had a good recovery.

Conclusions: These four patients support the use of recombinant activated factor VII as a useful adjunct to control massive life-threatening bleeding during pediatric neurosurgical procedures when other means failed. However, the data are still limited in children, and more extensive research is needed to define the indications of recombinant activated factor VII in massive surgical hemorrhage in low-weight children. (Pediatr Crit Care Med 2007; 8:576–579)

Key Words: children; recombinant activated factor VII; hemorrhage; hemostasis; neurosurgical intensive care

- 4 детей с массивной операционной кровопотерей и проблемами с гемостазом. Фактор дает быстрый эффект когда другие методы уже не эффективны.

J Neurosurg (1 Suppl Pediatrics) 104:55–58, 2006

Recombinant activated factor VII in the treatment of near-fatal bleeding during pediatric brain tumor surgery

Report of two cases and review of the literature

Matthias Hartmann, M.D., Christoph Sucker, M.D., and Martina Messing, M.D.

Departments of Anesthesiology and Neurosurgery, and Institute for Hemostasis and Transfusion Medicine, University Hospital Düsseldorf, Germany

✓Recombinant activated factor VII (rFVIIa) was successfully used in two pediatric cases to control microvascular bleeding during brain tumor surgery. The agent demonstrated a marked effect on the intraoperative blood coagulation after failure of conventional therapy with fresh-frozen plasma, platelet concentrates, and inhibition of the fibrinolytic system. Remarkably, rFVIIa was effective in the present cases in which assessment of hemostasis yielded normal results. The use of rFVIIa should be considered in otherwise untreatable microvascular bleeding in pediatric neurosurgery.

Key Words • **intraoperative bleeding** • **brain tumor** • **recombinant activated factor VII** • **pediatric neurosurgery**

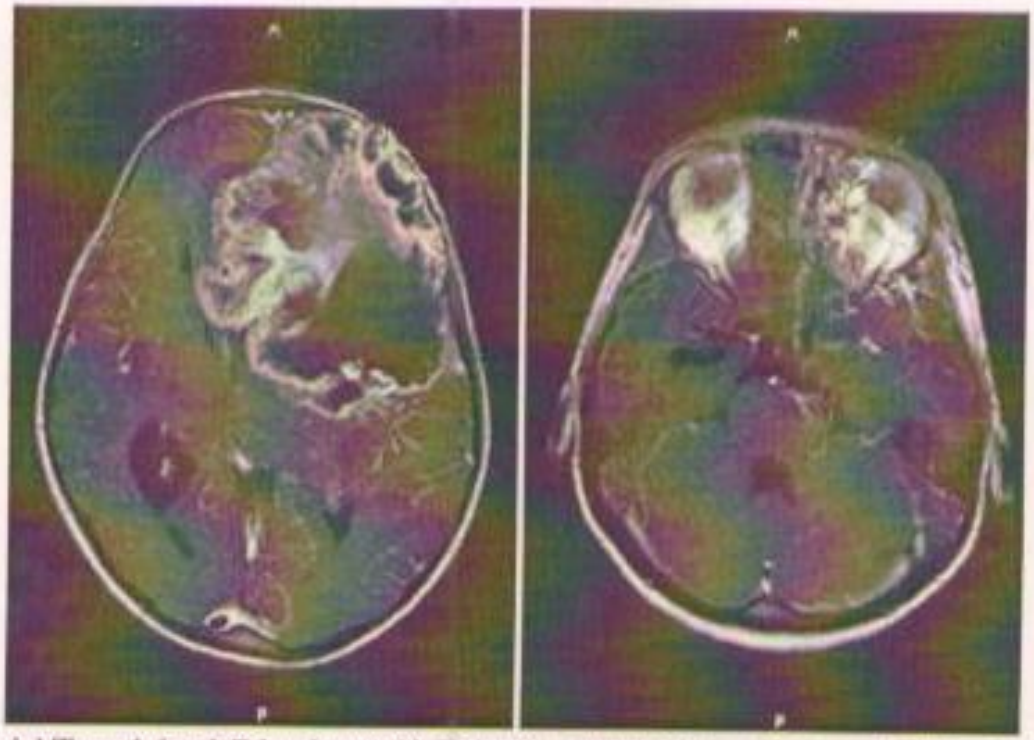


FIG. 1. Case 1. Axial T_1-weighted Gd-enhanced MR images obtained in a 9-year-old girl. *Left:* A large, cystic, hypervascularized tumor of the left frontotemporal region with marked mass effect on surrounding structures. *Right:* Hypervascularization of the left orbital and periorbital region can be seen.

were contraindicated in view of the risk of brain herniation.

The findings in our two cases support the use of rFVIIa in pediatric neurosurgery, particularly when conventional approaches to stop bleeding fail. Prospective randomized data regarding this issue, however, are missing.[11] Randomized prospective studies are needed because of the enormous cost of the therapy: the price of a 4.8-mg vial of rFVII is approximately $7000 US. Fortunately, a number of prospective randomized studies of rFVIIa applied in different settings have been initiated.[2] In the near future these studies will show if the use of rFVIIa as a universal hemostatic agent indeed leads to new therapeutic options in cases of diffuse bleeding.[8]

Наш материал

Тип опухоли	Количество
эпендимома	1
астроцитома	2
Хориоидная опухоль	4
менингиома	1
другие	1

Характеристика по другим признакам:

- Возраст детей от 6 месяцев до 15 лет.
- Кровопотеря от 100% до 200% ОЦК.
- Летальность 33,3% (3 из 9), причем из 3 умерших только один умер в ближайшем послеоперационном периоде.

Клиническое наблюдение №1

Ребенок П., 6 мес. Вес 8 кг. Гистологический диагноз «Хориоидкарцинома».

Кровопотеря в ходе операции составила 1500 мл, около 200% должного ОЦК.

НовоСевен ввели дважды в ходе операции в дозе 140 мкг/кг.

Клиническое наблюдение № 2

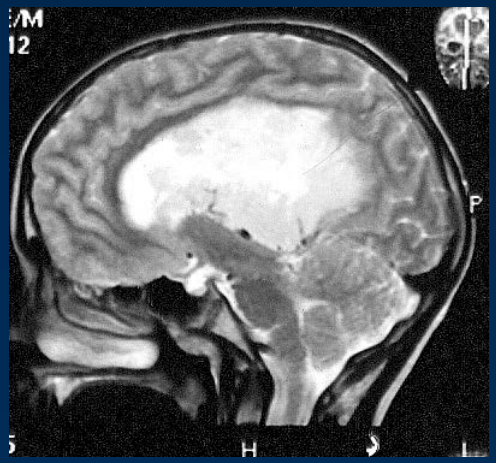
Больной Х., 10 лет, вес 32 кг.

Операционная кровопотеря около 4000 мл, 1,5 должного ОЦК.

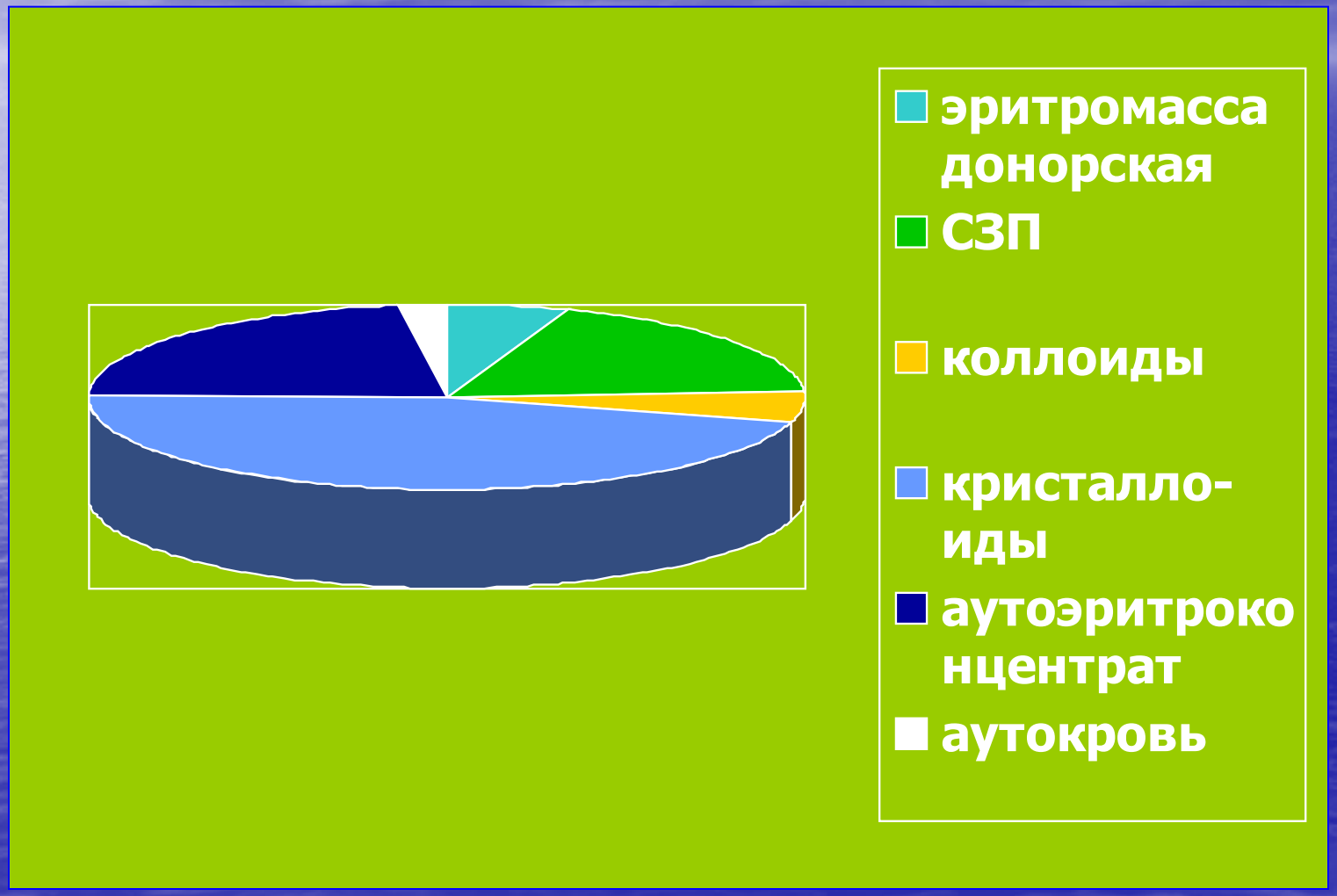
Использовались изоволемическая гемодилюция, реинфузия собственных отмытых эритроцитов, ингибиторы фибринолиза.

Новосевен использован в дозе 80 мкг/кг дважды с интервалом в 1 час.

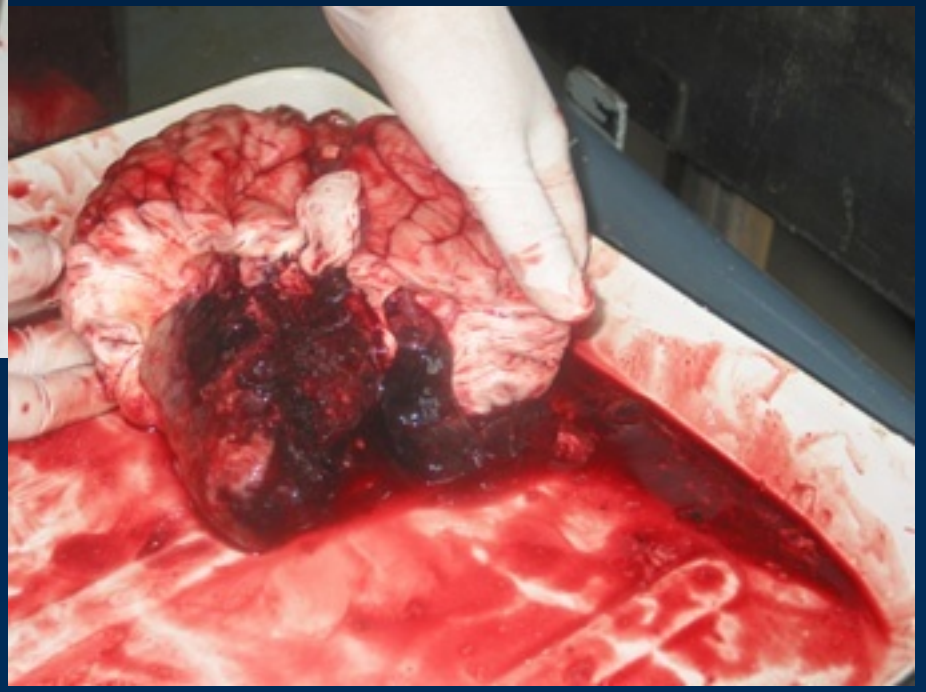
Клиническое наблюдение № 2



Клиническое наблюдение № 2, структура инфузионной терапии



Клиническое наблюдение № 2



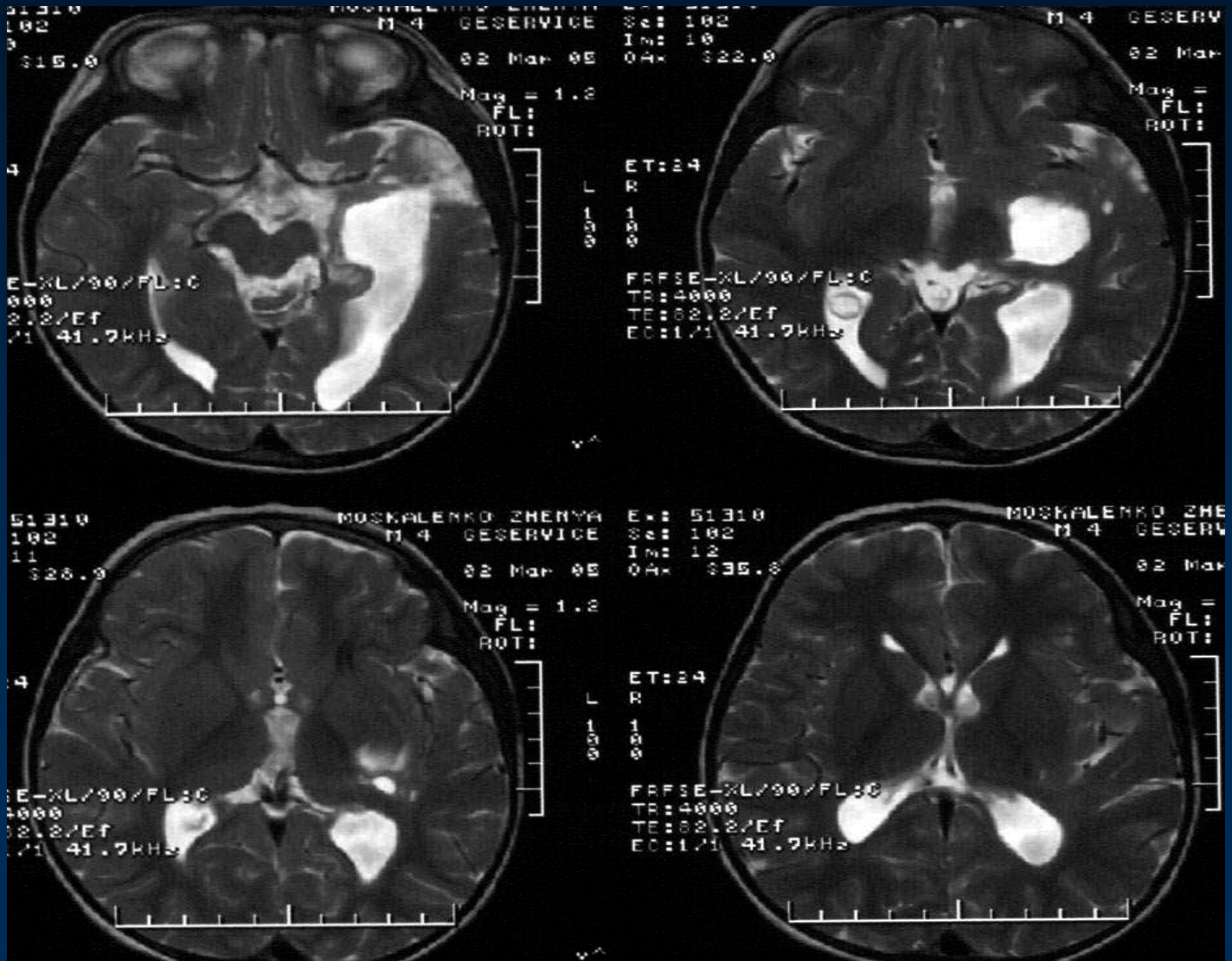
Клиническое наблюдение № 3.

Больной М., 3 года, вес 19 кг. Гистологический диагноз «Хориоидпапиллома». Операционная кровопотеря составила около 4000 мл., причем 3000 мл за 1 час.

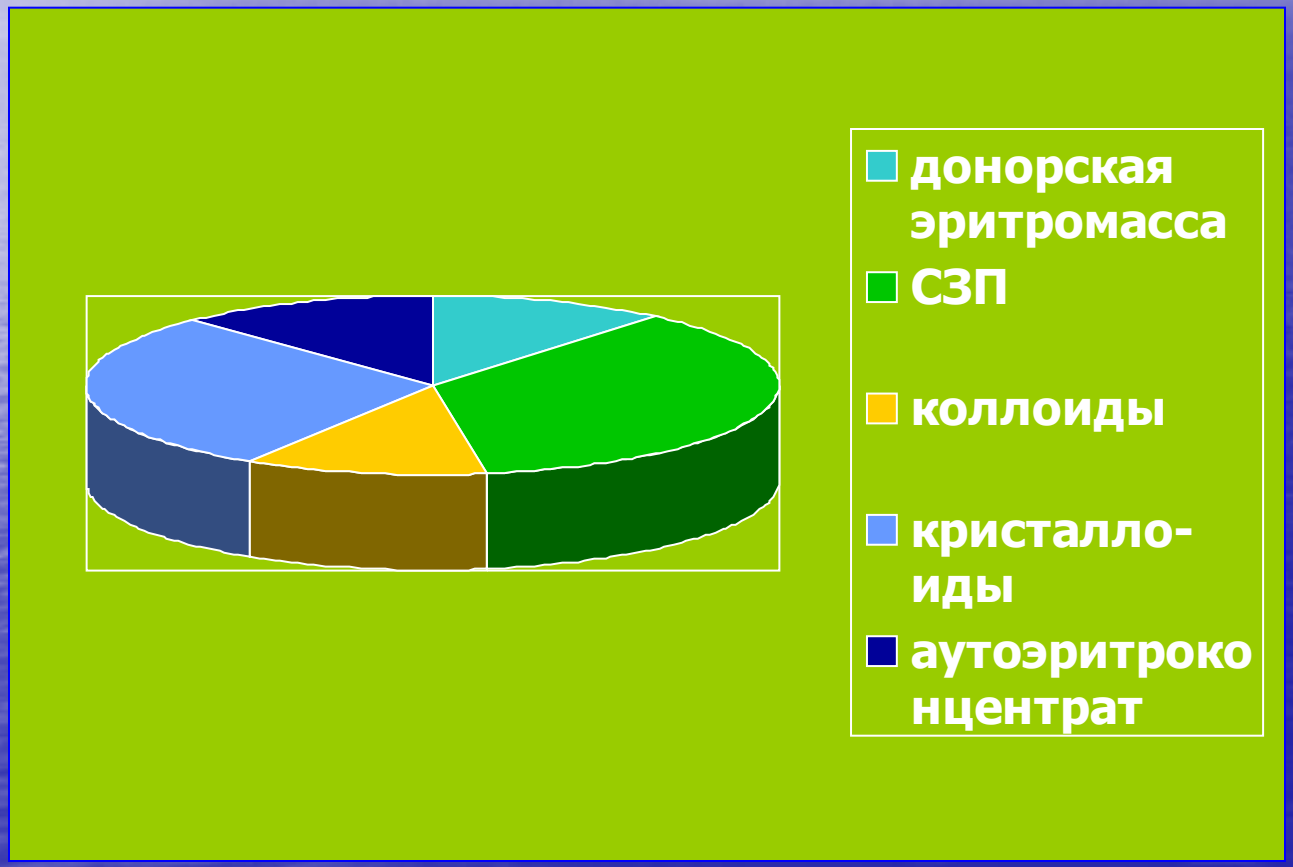
Использовали реинфузию собственных отмытых эритроцитов, введение ингибиторов фибринолиза.

Новосевен ввели однократно в дозе 120 мкг/кг.

Клиническое наблюдение № 3



Клиническое наблюдение № 3. Структура инфузионной терапии.



Клиническое наблюдение № 4.

Ребенок К., 14 лет. Вес 19 кг.

Гистологический диагноз «Анапластическая менингеома».

Кровопотеря 5500 мл, т.е. около 130% ОЦК.

Использовали изоволемическую гемодилюцию, реинфузию собственных отмытых эритроцитов, введение ингибиторов фибринолиза.

Новосевен ввели однократно в дозе 50 мкг/кг.

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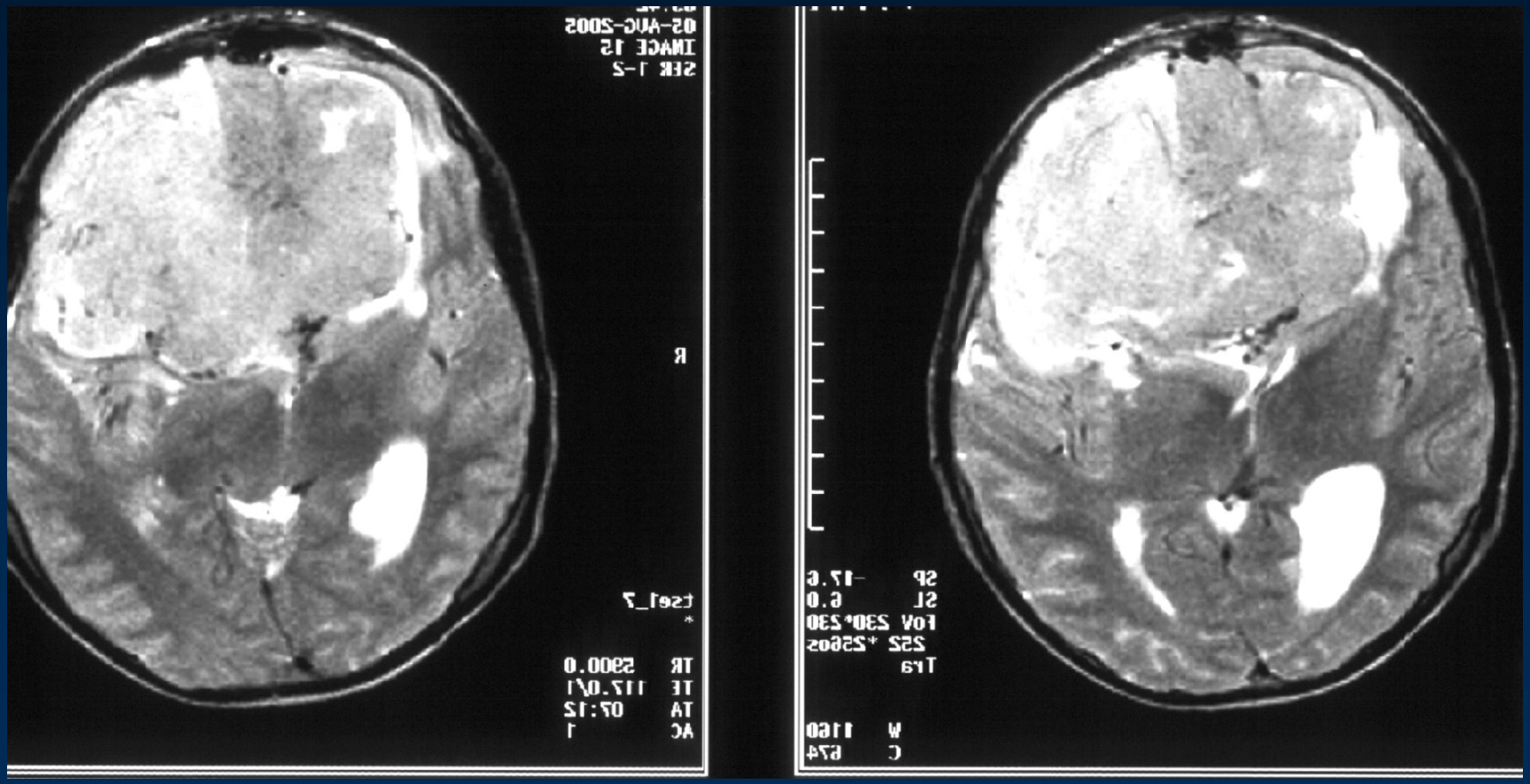
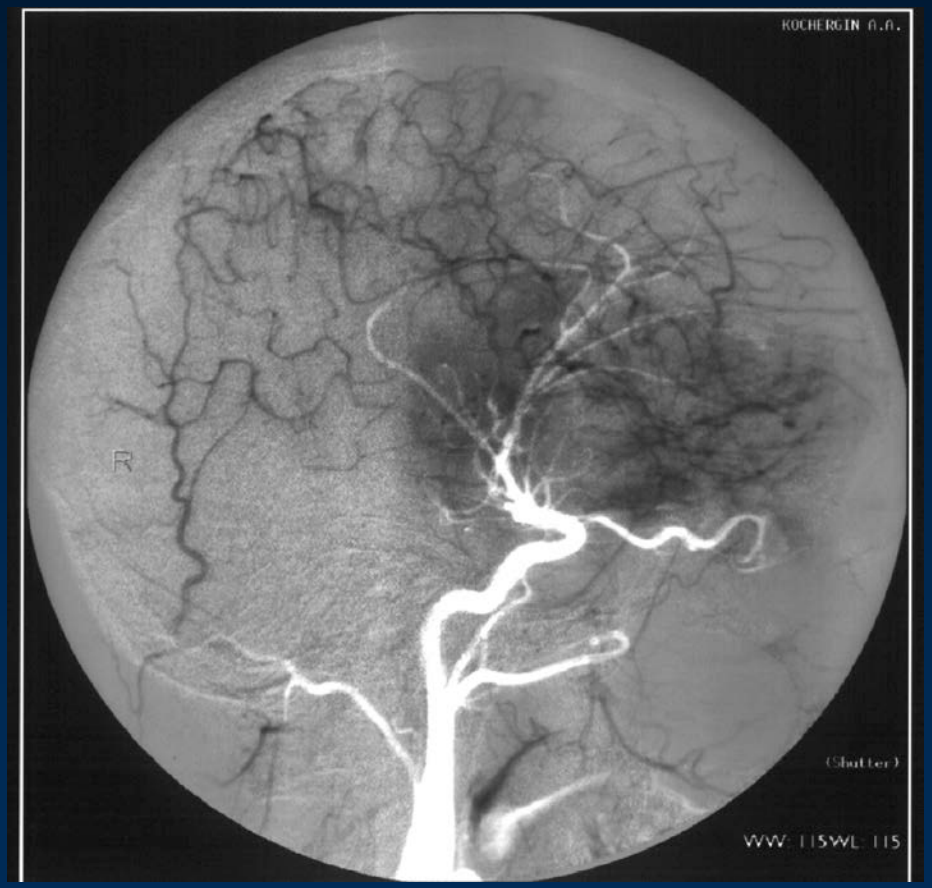
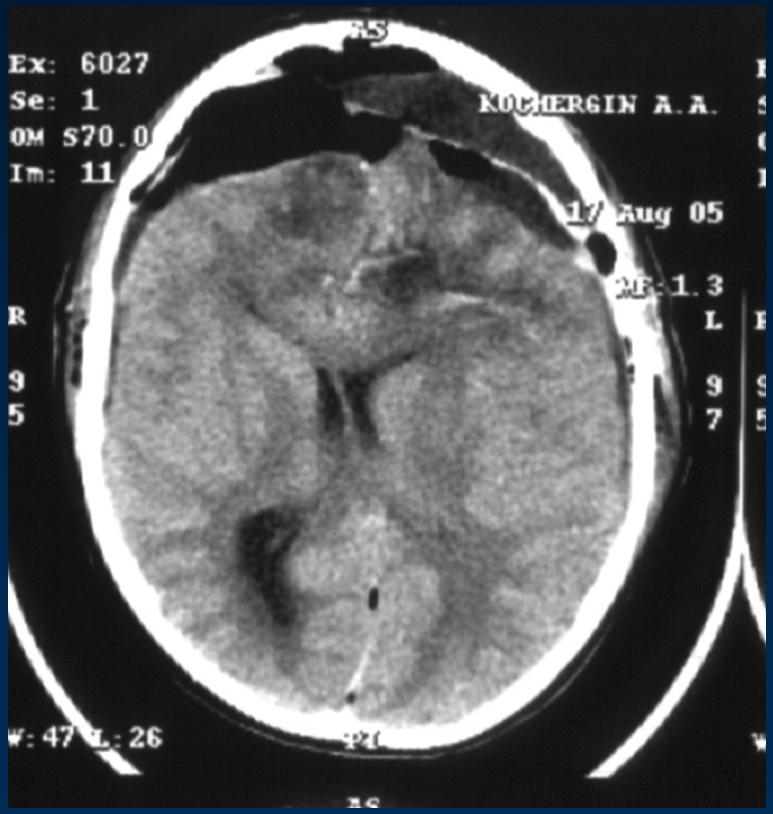


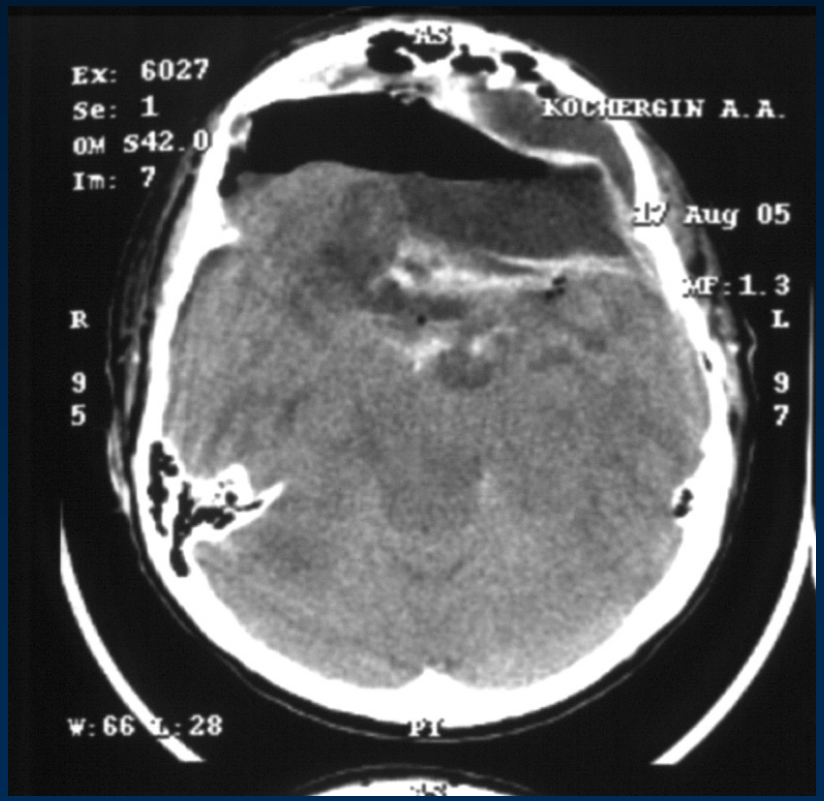
Клиническое наблюдение № 4. Ангиография до операции.



Клиническое наблюдение №4. Структура инфузионной терапии.

Клиническое наблюдение № 4. КТ после операции.





Клиническое наблюдение № 5.

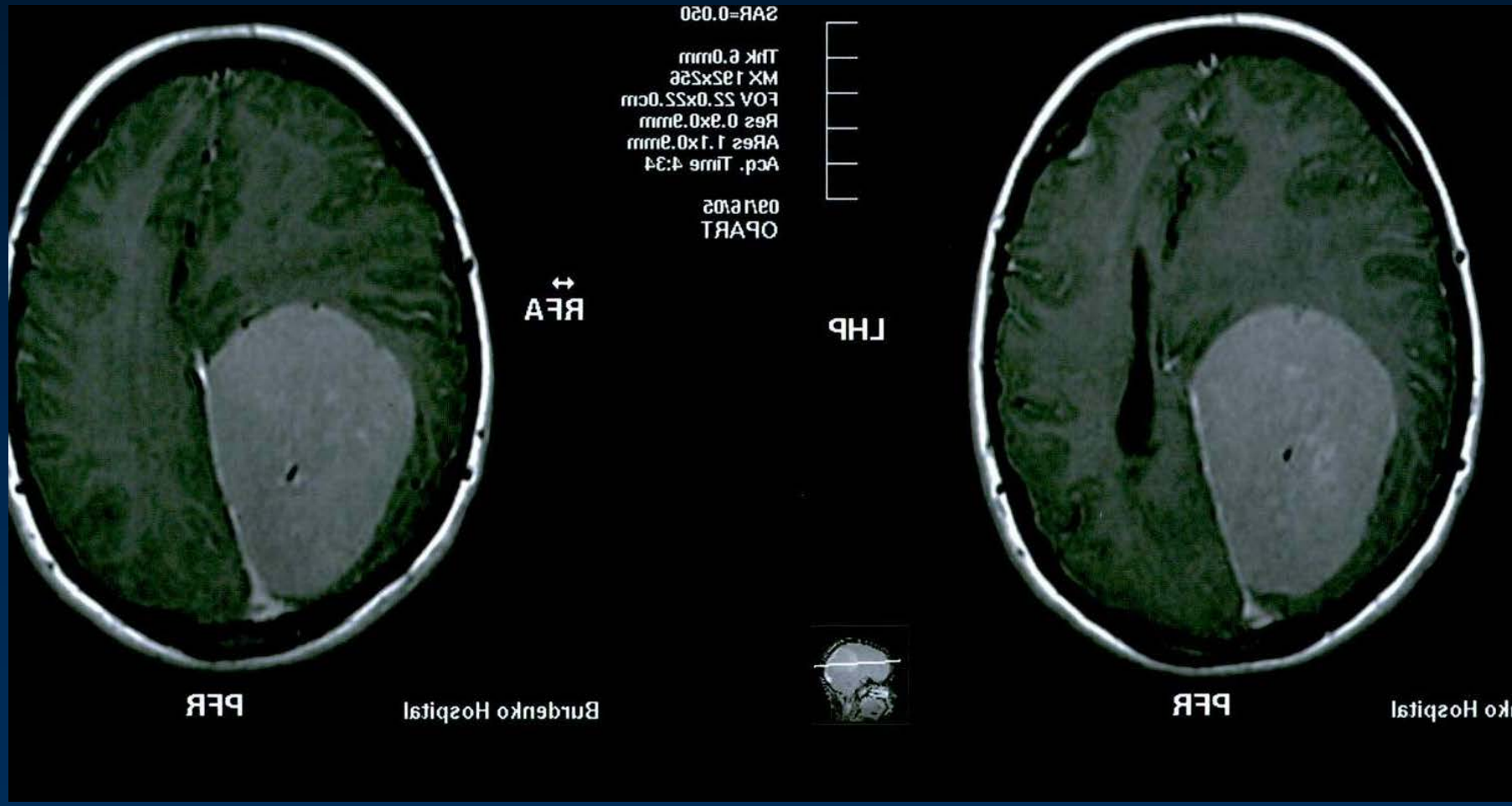
Больной Щ., 15 лет, вес 43 кг. Гистологический диагноз «Менингеома».

Операционная кровопотеря составила около 5000 мл., причем 1500 мл на доступе.

Использовали реинфузию собственных отмытых эритроцитов, введение ингибиторов фибринолиза.

Новосевен ввели дважды в дозе 60 мкг/кг.

Клиническое наблюдение № 5. КТ до операции.



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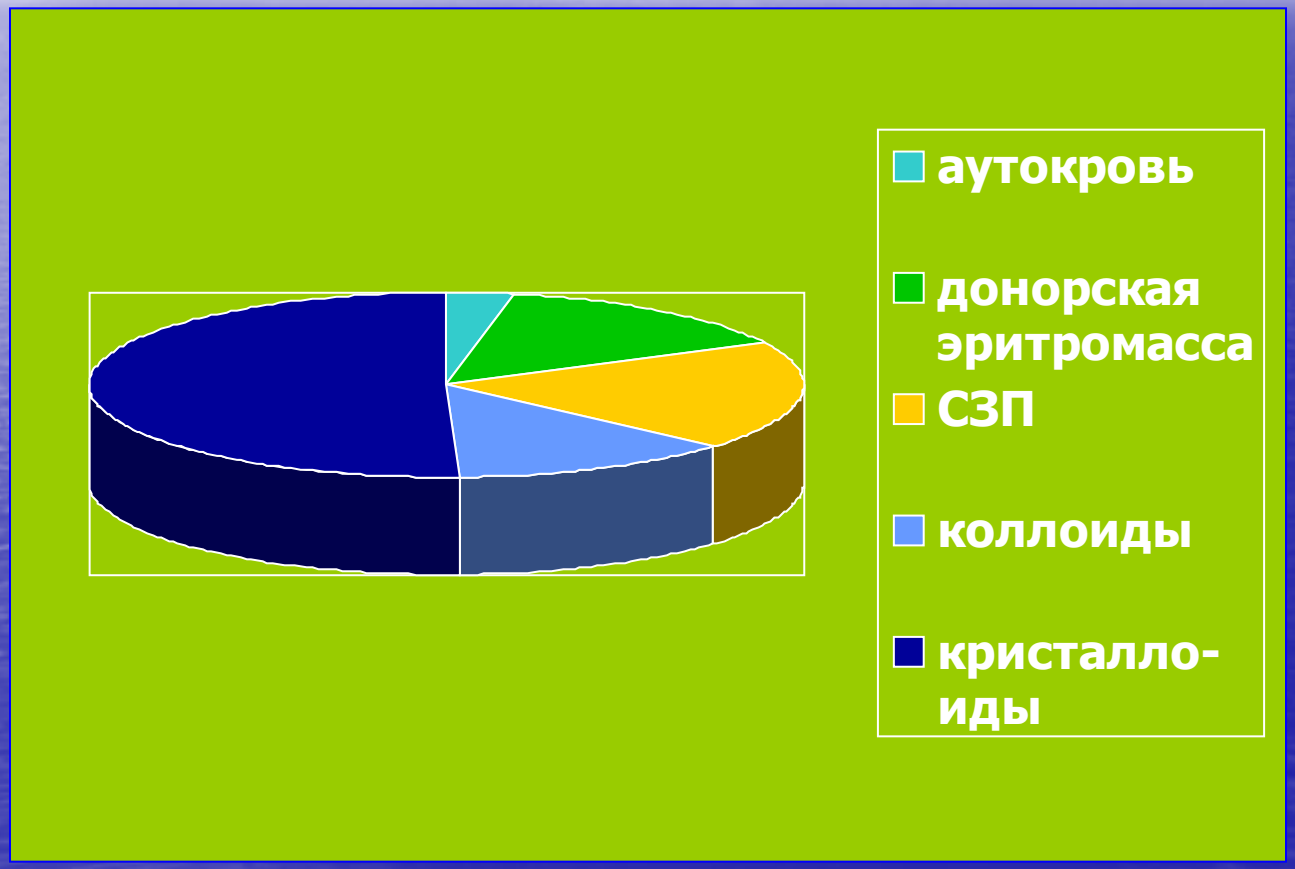

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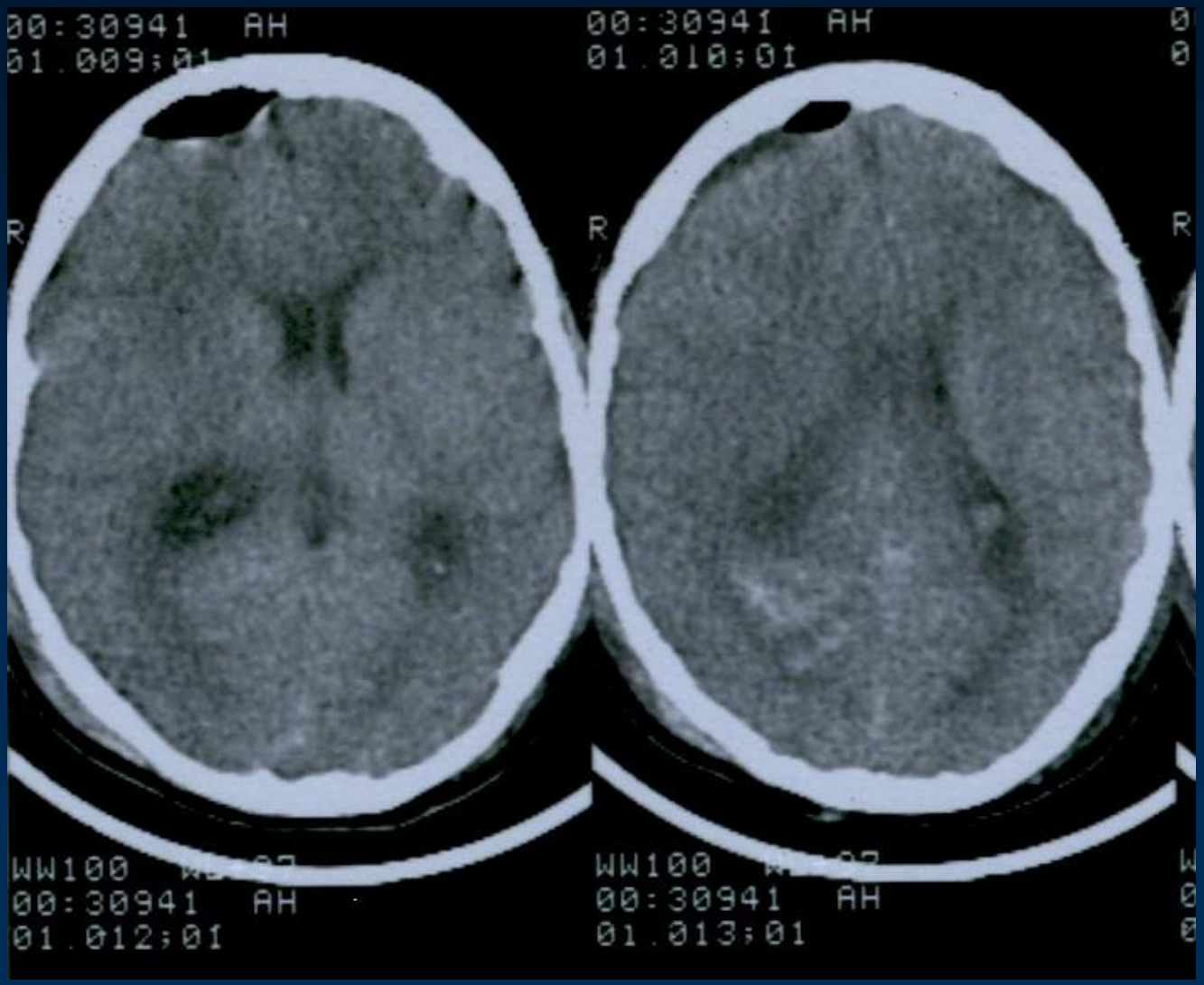


Кровопотеря в хирургии опухолей головного мозга у детей грудного возраста

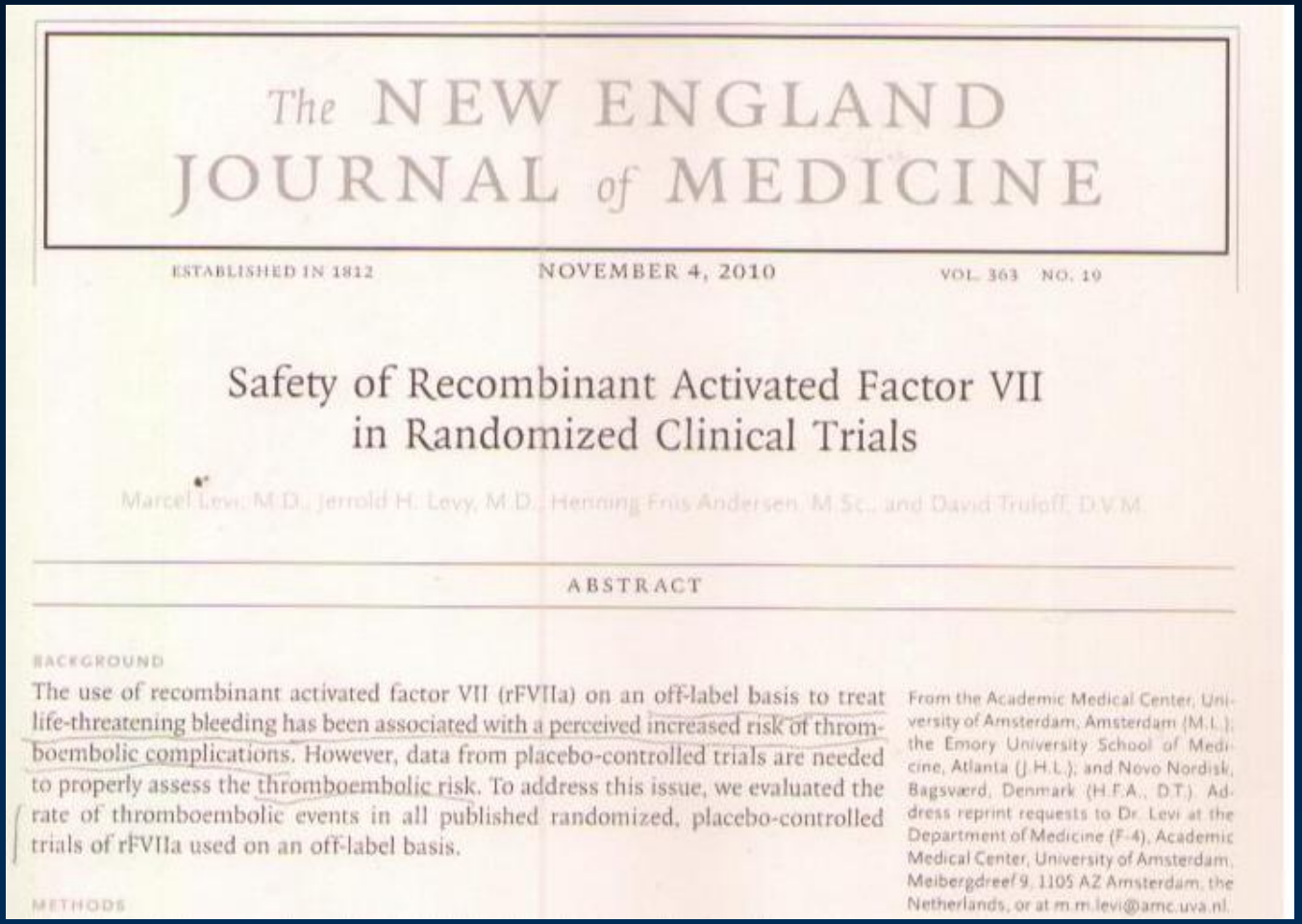
К.Б. МАТУЕВ[1, 2], проф. С.К. ГОРЕЛЫШЕВ[1, 2], проф. А.Ю. ЛУБНИН[1], к.м.н. Н.В. ЛЕМЕНЕВА[1], С.С. СОРОКИН[1]

[1]ФГБУ «НИИ нейрохирургии им. акад. Н.Н. Бурденко» (дир. — акад. РАН и РАМН А.Н. Коновалов) РАМН, Москва; [2]ГБОУ ДПО «РМАПО» (ректор — акад. РАМН Л.К. Мошетова), Москва

Функциональная незрелость всех органов и систем обусловливает высокий риск осложнений в хирургии опухолей головного мозга у детей грудного возраста. Одним из наиболее грозных осложнений является массивная операционная кровопотеря и развивающиеся на ее фоне тяжелые нарушения гемостаза. В современных сериях наблюдений периоперационная летальность у этих детей варьирует от 13 до 33%. Цель работы — на основании анализа топографии, морфологии опухоли и особенностей операций определить группы риска кровопотери в хирургии опухолей головного мозга у детей грудного возраста и предложить оптимальные варианты хирургической тактики. В основе анализа — ретроспективное (2000—2007 гг., *n*=39) — проспективное (2008—2010 гг., *n*=41) исследование. К группе *низкого риска* по операционной кровопотере относятся опухоли вне зависимости от размеров следующих топографогистологических форм: глиомы хиазмы; хориоидпапилломы; все опухоли мозжечка и IV желудочка. К группе *среднего риска* по операционной кровопотере относятся большие (> 4 см) злокачественные опухоли супратенториальной локализации (преимущественно анапластические астроцитомы и эпендимомы) с кистозным компонентом. К группе *высокого риска* по операционной кровопотере относятся большие (>4 см) солидные злокачественные опухоли (преимущественно хориокарциномы, реже эпендиобластомы, пинеобластомы, АТРО). При операционной кровопотере, превышающей 300% расчетного ОЦК, развиваются стойкие нарушения коагуляционного гемостаза, которые могут привести к неконтролируемому кровотечению и смерти на операционном столе либо послеоперационному кровотечению. Снижение объема операционной кровопотери возможно за счет совершенствования как хирургической техники, так и анестезиологического пособия. К первому относится предоперационная эмболизация афферентных сосудов, тщательное планирование доступа, в том числе с использованием нейронавигации; глубокая коагуляция стромы опухоли во время «дебалкинга», первоочередная коагуляция питающих опухоль сосудов; двухэтапное проведение операции, а также оптимизация скорости удаления опухоли. Применение современных методов кровесбережения в сочетании с особенностями хирургической тактики позволило снизить общую операционную и послеоперационную смертность с 13 до 5%.

Ключевые слова: *опухоли головного мозга у детей грудного (infants) возраста, хирургия, массивная операционная кровопотеря, большие хориокарциномы у детей грудного возраста.*

Безопасность rVIIa – тромбоэмболические осложнения



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Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Fris Andersen, M.Sc., and David Truloff, D.V.M.

ABSTRACT

BACKGROUND

The use of recombinant activated factor VII (rFVIIa) on an off-label basis to treat life-threatening bleeding has been associated with a perceived increased risk of thromboembolic complications. However, data from placebo-controlled trials are needed to properly assess the thromboembolic risk. To address this issue, we evaluated the rate of thromboembolic events in all published randomized, placebo-controlled trials of rFVIIa used on an off-label basis.

METHODS

From the Academic Medical Center, University of Amsterdam, Amsterdam (M.L.); the Emory University School of Medicine, Atlanta (J.H.L.); and Novo Nordisk, Bagsværd, Denmark (H.F.A., D.T.). Address reprint requests to Dr. Levi at the Department of Medicine (F-4), Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at m.m.levi@amc.uva.nl.

Table 2. **Odds Ratios for Thromboembolic Events.**

Thromboembolic Event	rFVIIa (N = 2583)	Placebo (N = 1536)	Odds Ratio (95% CI)*	P Value
	number (percent)†			
All events	264 (10.2)	134 (8.7)	1.17 (0.94–1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70–1.23)	0.61

* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.
† The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received the assigned study drug.

Table 3. **Arterial Thromboembolic Events with a Rate Greater Than 0.5%.**

Variable	rFVIIa (N = 2583)	Placebo (N = 1536)	Odds Ratio (95% CI)*	P Value
	number (percent)			
All arterial thromboembolic events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Coronary events	76 (2.9)	17 (1.1)	2.39 (1.39–4.09)	0.002
Acute coronary syndromes	57 (2.2)	11 (0.7)		
Increased troponin level	19 (0.7)	6 (0.4)		
Cerebrovascular events	45 (1.7)	20 (1.3)	1.27 (0.74–2.17)	0.39
Cerebral infarction	44 (1.7)	19 (1.2)		
Hemiparesis†	1 (<0.1)	1 (<0.1)		

* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.
† Computed tomographic confirmation of thrombosis was not obtained for the two cases of hemiparesis.

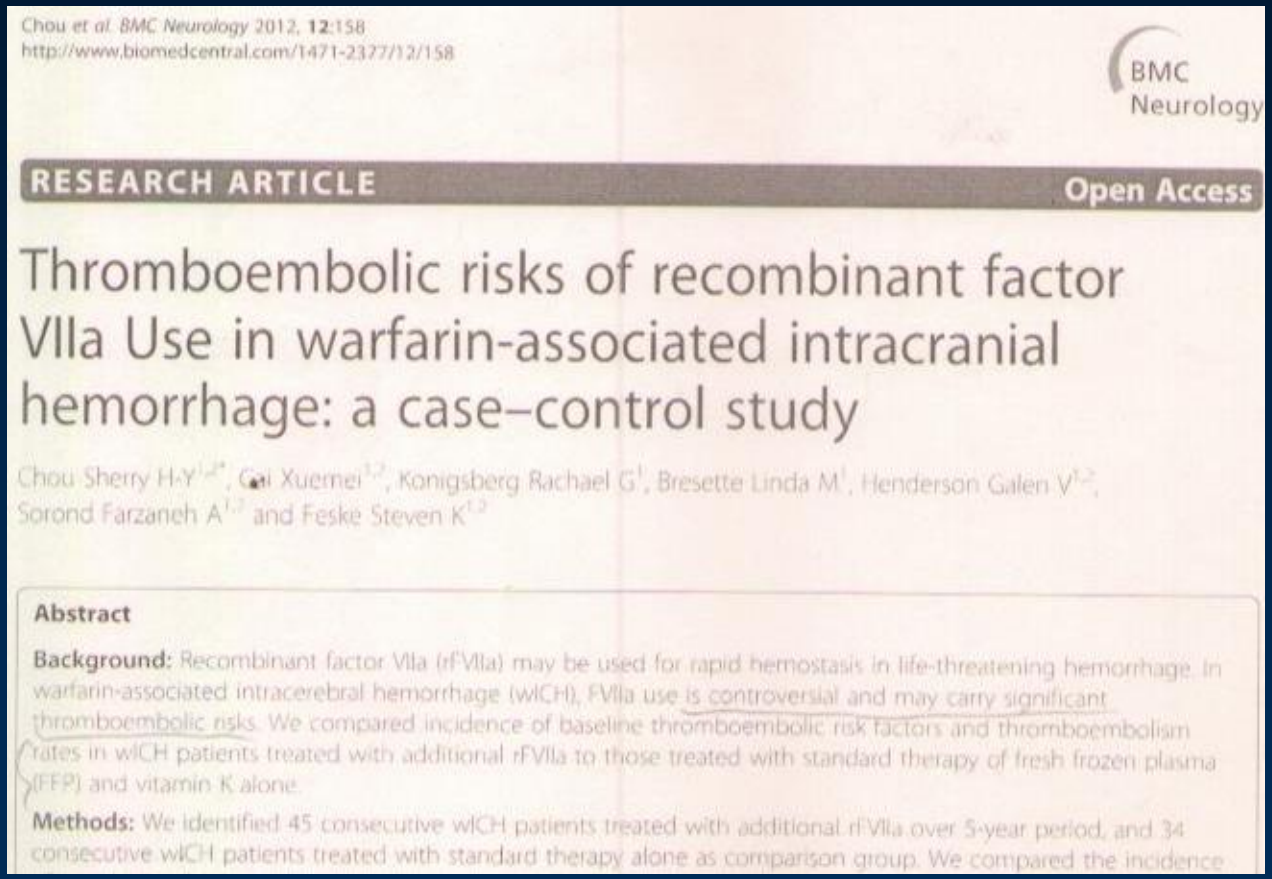
Table 4. **All Arterial Thromboembolic Events, According to Age.**

Age Group	rFVIIa	Placebo	Odds Ratio (95% CI)*	P Value†
	no./total no. (%)‡			
<18 yr	1/70 (1.4)	1/51 (2.0)		
18–64 yr	73/1764 (4.1)	34/1107 (3.1)	1.36 (0.89–2.08)	0.15
≥65 yr	67/742 (9.0)	14/372 (3.8)	2.43 (1.34–4.41)	0.003
65–74 yr	33/427 (7.7)	8/225 (3.6)	2.12 (0.95–4.71)	0.07
≥75 yr	34/315 (10.8)	6/147 (4.1)	3.02 (1.22–7.48)	0.02

* Odds ratios were calculated by means of logistic regression with adjustment for indication.
† The P value was not calculated for the first age group because there were only two events.
‡ The percentage of thromboembolic events was calculated as the number of patients with events as a proportion of the number of patients who received a study drug.

risk of arterial thromboembolic

Безопасность rVIIa – тромбоэмболические осложнения



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RESEARCH ARTICLE Open Access

Thromboembolic risks of recombinant factor VIIa Use in warfarin-associated intracranial hemorrhage: a case–control study

Chou Sherry H-Y[1,2*], Cai Xuemei[1,2], Konigsberg Rachael G[1], Bresette Linda M[1], Henderson Galen V[1,2], Sorond Farzaneh A[1,2] and Feske Steven K[1,2]

Abstract

Background: Recombinant factor VIIa (rFVIIa) may be used for rapid hemostasis in life-threatening hemorrhage. In warfarin-associated intracerebral hemorrhage (wICH), FVIIa use is controversial and may carry significant thromboembolic risks. We compared incidence of baseline thromboembolic risk factors and thromboembolism rates in wICH patients treated with additional rFVIIa to those treated with standard therapy of fresh frozen plasma (FFP) and vitamin K alone.

Methods: We identified 45 consecutive wICH patients treated with additional rFVIIa over 5-year period, and 34 consecutive wICH patients treated with standard therapy alone as comparison group. We compared the incidence

Table 2 Incidences of Thromboembolic Complications

	FVIIa Group (n = 45)	Comparison Group (n = 34)	p-value
Troponin elevation	21 (47%)	14 (41%)	0.53
Clinically Significant Troponin Elevation (Troponin > 1.0 ng/dL)	6 (13%)	2 (6%)	0.52
New EKG changes	19 (42%)	6 (18%)	0.06
T-wave abnormality	8 (18%)	1 (3%)	
ST abnormality	4 (9%)	3 (9%)	
Conduction block	1 (2%)	0	
Arrhythmia	3 (7%)	1 (3%)	
QTc prolongation	2 (5%)	1 (3%)	
Troponin elevation with EKG Changes	2 (4%)	0	0.29
DVT/PE	1 (2%)	3 (9%)	0.18
Stroke	1 (2%)	0	0.38

Table 3 Clinical Outcomes

	FVIIa group (n = 45)	Comparison Group (n = 34)	p-value
Mean INR at 3 h	0.98 [0.90 – 1.06]	1.63 [1.40 – 1.86]	0.0001
Mean INR at 6 hours	1.10 [1.00 – 1.20]	1.51 [1.41 – 1.61]	<0.0001
Mean units of FFP transfused	3 [2.1 – 3.9]	5 [3.6 – 6.3]	0.003
Surgical hematoma evacuation	17 (38%)	6 (18%)	0.05
Survival after surgical hematoma evacuation	14 (31%)	4 (12%)	0.04
In-hospital death	16 (36%)	6 (18%)	0.07
Withdrawal of life-prolonging care	14 (31%)	6 (18%)	0.17

Conclusions

Warfarin-associated ICH patients have high prevalence of baseline thromboembolic risk factors and high prevalence of post-ICH troponin elevation regardless of rFVIIa use. Recombinant FVIIa use does not appear to increase the risk of cardiac or extra-cardiac thromboembolic events following wICH in our patient cohorts. Pre-existing CAD and abnormal baseline EKG are risk factors for clinically significant MI post-wICH regardless of rFVIIa use. Recombinant factor VIIa is not associated with prohibitively high incidence of thromboembolic complications while it is associated with decreased FFP use and higher survival rate after hematoma evacuation, making it a potential wICH therapeutic agent. Larger prospective randomized studies are necessary to determine whether rFVIIa or PCC use improves outcome in wICH patients.

Стоимость

- Цена вопроса – 2 USD за 1 мкг препарата.
- Даже при использовании небольших доз (30 мкг/кг) у среднестатистического пациента весом 70 кг это составляет 4200 USD.
- Причем цена отечественного и датского препаратов отличаются мало.

Выводы

- В настоящее время человечество получило в свое распоряжение новый высоко эффективный гемостатический агент – рекомбинантный активированный VII фактор.

- Исходно одобренный для лечения гемофиликов, он в настоящее время получил исключительно широкое клиническое применение в лечении коагулопатий, в том числе обусловленных массивной кровопотерей различного генеза и травмой.

Выводы

- Благодаря своему особому механизму действия, rVIIa позволяет добиться быстрой остановки кровотечения тогда, когда традиционные подходы уже не эффективны.

- В этой связи он используется практически во всех областях хирургии, при проведении вмешательств, осложненных массивной операционной кровопотерей.

Выводы

- В нейрохирургии применение rVIIa дает особые серьезные преимущества у пострадавших с тяжелой ЧМТ, больных со спонтанными внутримозговыми кровоизлияниями, спинальной патологией и при удалении больших богато кровоснабжаемых опухолей мозга, в особенности у детей, у которых выраженные нарушения гемостаза на фоне массивной кровопотери развиваются особенно быстро.

Выводы

- Для достижения эффекта от использования rVIIa необходима предварительная коррекция ацидоза, гипокальциемии, гипофибриногенэмии и тромбоцитопении.

- В связи с ограниченностью эффекта препарата по времени, для достижения надежного гемостаза может потребоваться его повторное введение через 2 – 3 часа.