E. 結論

術中の大量出血時により血小板数やフィブリノーゲン値が低下し、止血凝固能が低下した場合、血小板製剤と新鮮凍結血漿の輸血だけによる補充では不十分で、クリオプレシピテート製剤など濃縮製剤の投与で止血凝固能を改善させることによって良好な止血を達成できる可能性が考えられた。あわせて、人工心肺前の自己血小板採取が総輸血使用量を減少させうると考えられた。

G. 研究発表

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2. 学会発表

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H. 知的財産権の出願・登録状況

なし

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表レイアウト

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
稲田英一	緊急輸血と大量輸血	認定輸血検査技師制度協議会カリキュラム委員会	スタンダード輸血検査テキスト第2版	医歯薬出版	東京	2007	211-218

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yamamoto K, Kojima T, Takeshita K, Matsushita T, Takamatsu J	Pitavastatin attenuates the upregulation of tissue factor in restraint-stressed mice	Thrombosis Research	120	143-144	2007
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Kajiguchi M, Kondo T, Izawa H, Kobayashi M, Yamamoto K, Shintani S, Numaguchi Y, Naoe T, Takamatsu J, Komori K, Murohara T	Safety and efficacy of autologous progenitor cell transplantation for therapeutic angiogenesis in patients with critical limb ischemia	Circulation Journal	71	196-201	2007
池山明子、金 壁年、高尾のぞみ、角渕浩央、小林 信、富田彰、鈴木章吾、橋本 篤、浅野市子、梅田亜希子、市川崇、梶田博史、中澤朋子、辻 里花、矢野 隆，須藤悠介、滝 和美、西脇公俊、島田康弘	大量出血－大量出血時の凝固障害について－	臨床麻酔	31	753-758	2007
高松純樹	「周術期における輸血療法：総論」	週間医学の歩み	224	183-189	2008
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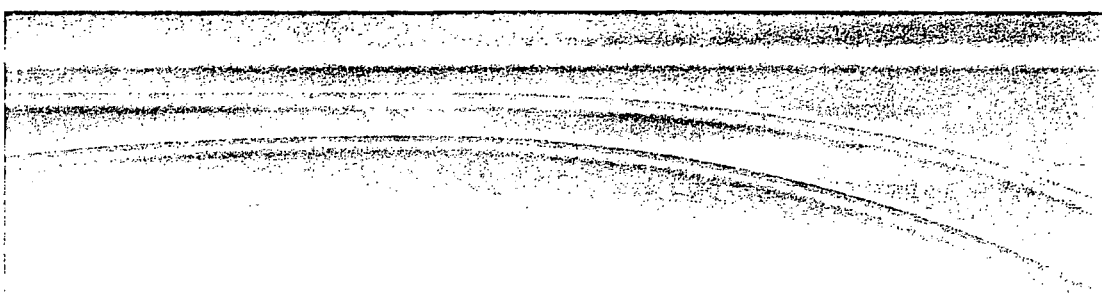
Ⅳ. 研究成果の刊行物・別刷

スタンダード
輸血検査テキスト

第2版

認定輸血検査技師制度協議会カリキュラム委員会　編集



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B－緊急輸血と大量輸血

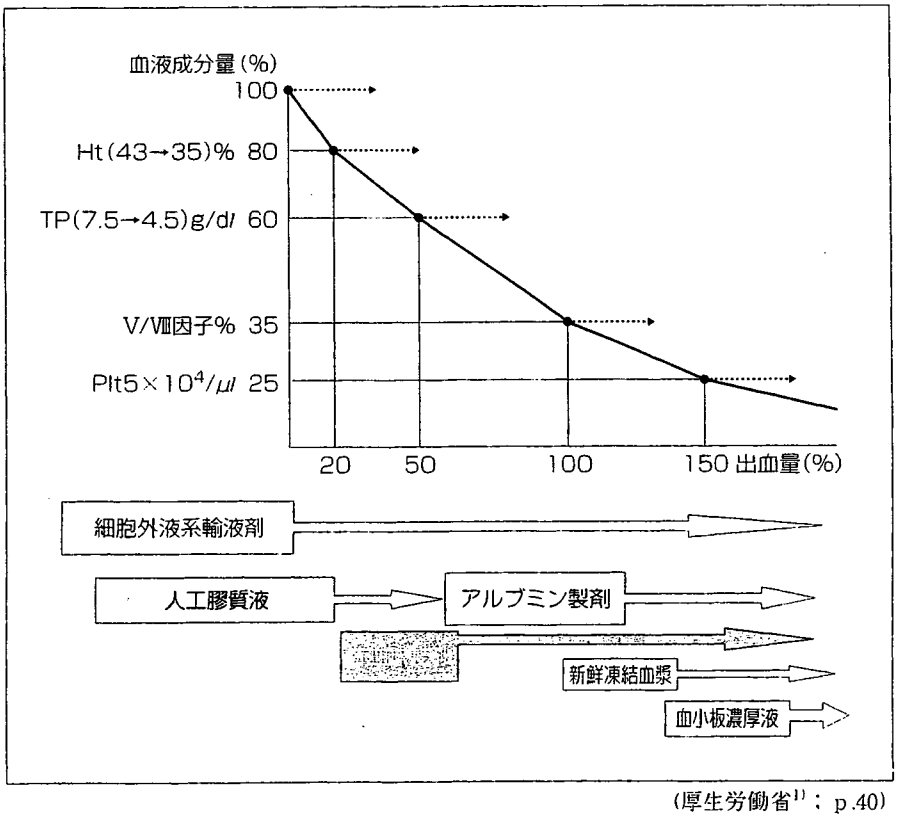
大量輸血は通常，24時間以内に循環血液量を超えるような出血と定義される．急速な出血の定義はないが，100m*l*/分を超えるような出血がある場合には，処置が遅れれば致死的となる可能性があり，ここでは便宜上100m*l*/分（小児に換算すれば1.5m*l*/kg/分以上）の出血を急速出血と定義する．

①緊急輸血，大量輸血時の検査

急速な出血があり，緊急に輸血が必要な場合や大量輸血時の検査は，(1) 血液に関する検査，(2) 循環血液量など血行動態に関する検査，そして (3) 肺を含むその他の臓器の検査に分けて考えることができる．

(1) 血液に関する検査

出血に伴い，血漿およびすべての血球成分が失われる（**図Ⅵ・B-1**）．血算および血液凝固系検査が必要となるが，出血後，ただちにこれらの検査結果が異常になるわけではないことに注意する．血液が失われた後，血管内に細胞外液が流入したり，循環血液量を補うために輸液が行われることにより，血液希釈が起きる．結果が安定するまでは30分程度が必要と考えられている．しかし，急速出血時や活動性出血がある場合には，そのような時間を待たずに検査を行う必要がある．したがって，得られた値はあくまで途中経過を示すものであり，検査結果が得られた頃には状況はさらに進行しているという仮定のもとに輸血の判断を下す必要がある．また，急速な出



(厚生労働省[1]：p.40)

図Ⅵ・B-1　出血に伴う血液成分の変化と輸液・輸血製剤の基本

血があり，循環血液量を超えるような出血が短時間のうちに起きる可能性が高い場合には，検査結果を待たずに輸血する場合がある．その場合でも，検査のための採血だけは行っておく必要がある．輸血を開始した後に，あるいは処置後に検査結果を評価する．臨床的な出血傾向および検査結果の改善について評価する必要がある．

ヘモグロビン（Hb）値あるいはヘマトクリット（Hct）値の測定は必須である．血小板数やプロトロンビン時間（PT），活性化部分トロンボプラスチン時間（APTT），フィブリノゲン濃度は，循環血液量以上の出血があった場合に変化する．しかし，一般的には，出血量が循環血液量の半分を超えるような事態が起きた場合には測定し，状況を把握しておくことが多い．また，血小板数やPT，APTT，フィブリノゲン濃度は臨床的に出血傾向が認められる場合に，その原因を鑑別し，必要な輸血製剤を選択するために必要である．フィブリノゲン濃度の低下は，PTやAPTTに反映されないので注意する．

血小板輸血や新鮮凍結血漿輸注が必要となるのは，通常は循環血液量を超えるような出血が起きた場合であるが，それ以前に重大な出血傾向が出現する可能性もある．出血の原因となる疾患のために，播種性血管内凝固 disseminated intravascular coagulation（DIC）が出現し，出血傾向が出現する場合もある．したがって，血小板数や凝固系検査は経時的に測定する必要がある．DICが疑われる場合には，フィブリン分解産物（FDPやD-ダイマー），トロンビン-アンチトロンビン複合体，プラスミン-アンチプラスミン複合体の測定などが必要となる．

(2) 血行動態に関する検査

出血が起きた場合には，循環血液量不足を推定するために血圧や心拍数を頻回に測定する必要がある（**表Ⅵ・B-1**）．出血がそれほど急速でない場合には，尿量も循環血液量不足の推定に役立つ．血液の付着したガーゼの重量測定や血液吸引量から出血量の推定が困難な場合，あるいは出血が急速な場合には，動脈カテーテル，中心静脈カテーテル，さらには肺動脈カテーテルなどを挿入して，観血的測定が必要となる．

表Ⅵ・B-1　循環血液量減少の程度（%）とバイタルサインの変化

	クラス　Ⅰ	クラス　Ⅱ	クラス　Ⅲ	クラスⅣ
出血量	< 15%	15～30%	35～40%	> 40%
心拍数（回/分）	< 100	> 100	> 120	> 140
収縮期血圧（mmHg）	正常	正常	低下	低下
脈圧	正常	減少	減少	減少
呼吸数（回/分）	14～20	20～30	30～40	> 35
尿量（ml/時）	> 30	20～30	5～15	無尿
精神状態	正常，軽い不安あり	かなり不安感あり	不安，混迷	混迷，無気力

(3) 肺やその他の臓器の検査

大量出血が起こるような事態では，しばしば血液酸素化が悪化する．パルスオキシメータによる経皮的酸素飽和度測定や，動脈血液ガス分析により血液の酸素化を評価する．

血液ガスの測定も必要である．組織酸素化の障害により嫌気性代謝が進み，乳酸が産生され代謝性アシドーシスが進行する．乳酸濃度の上昇は，低潅流や組織低酸素症の1つの指標となる．

大量出血・輸血では後述するように，電解質異常が起こりうる．とくに高カリウム血症は心停止の原因ともなるので厳重な注意が必要である．

大量輸血では，しばしば低体温となるので，体温測定も重要である．

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② 緊急輸血，大量輸血時の血液製剤の選択

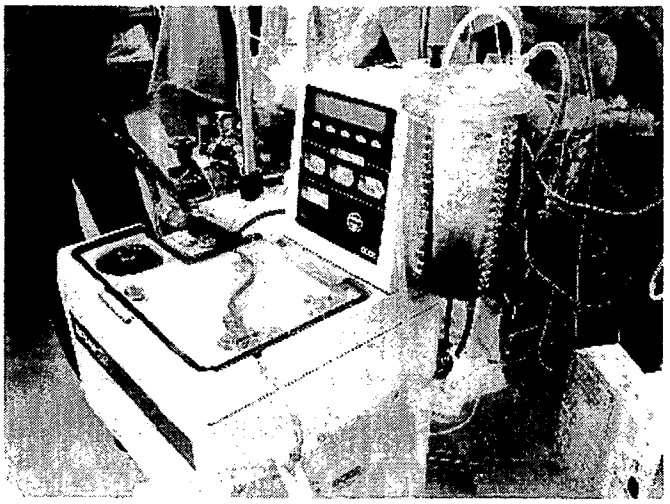
輸血にあたっては，出血量や血算，凝固系検査に従い，赤血球製剤や新鮮凍結血漿，赤血球濃厚液を投与する．また，大血管の破裂や外傷などでは，自己血回収が行われる場合があるので，これは別に述べる．循環血液量の50%以上の出血が起きた場合には，血漿量や膠質浸透圧維持の目的で，アルブミン製剤を投与する場合がある．

(1) 赤血球製剤

大量出血では，すべての血液成分が失われる．しかし，血小板減少症や凝固因子不足による出血傾向は，一般に循環血液量以上の出血が急速に起きないと出現しないため，多くの場合には，Hbを補う目的で赤血球製剤の輸血だけでよい．現在，日赤から供給される赤血球製剤の大部分はMAP加赤血球濃厚液である．Hbを補うためには，MAP加赤血球濃厚液で十分であり，全血をあえて用いる必要はない．

(2) 回収自己血（図Ⅵ・B-2[1]）

外傷や大動脈瘤破裂など清潔な部位からの出血の場合には，出血した血液を回収して，洗浄した後，赤血球浮遊液として返血することができる．血液回収装置やそれを操作する人間が必要となる．自己血回収は，悪性腫瘍手術や，腸管穿孔など細菌汚染がある手術では禁忌となる．



図Ⅵ・B-2　自己血回収装置
カリウムは照射した場合と照射なしの場合を示す．

(3) 新鮮凍結血漿

本来ならPTやPTT，フィブリノゲン濃度などを測定して，それらの値が新鮮凍結血漿の適応にかなっていれば新鮮凍結血漿を投与すべきであるが，急速出血が起きている場合には，そのような時間的な余裕はない．循環血液量以上の出血があり臨床的に出血傾向が認められる場合には，検査結果を待たず新鮮凍結血漿の投与を行う．

凝固因子の血中活性値が正常の20～30%あれば，止血効果が期待される（**表Ⅵ・B-2**[1]）．血中凝固因子活性を20～30%上昇させるのに必要な新鮮凍結血漿量は8～12ml/kgである．アメリカでは，10～15ml/kgの投与が推奨されている．

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表Ⅵ·B-2　凝固因子の生体内における動態と止血レベル

因子	止血に必要な濃度*1	生体内半減期	生体内回収率（%）	安定性（4℃保存）
フィブリノゲン	75～100mg/dl	3～6日	50	安定
プロトロンビン	40%	2～5日	40～80	安定
第Ⅴ因子	15～25%	15～36時間	80	不安定*2
第Ⅶ因子	5～10%	2～7時間	70～80	安定
第Ⅷ因子	10～40%	8～12時間	60～80	不安定*3
第Ⅸ因子	10～40%	18～24時間	40～50	安定
第Ⅹ因子	10～20%	1.5～2日	50	安定
第Ⅺ因子	15～30%	3～4日	90～100	安定
第Ⅻ因子	—	—	—	安定
第XIII因子	1～5%	6～10日	5～100	安定
フォン・ヴィレブランド因子	25～50%	3～5時間	—	不安定

*1：観血的処置時の下限値　（厚生労働省[1]；p.52）
*2：14日保存で活性は50%残存
*3：24時間保存で活性は25%残存

(4) 血小板濃厚液

活動性出血があり，5万/μl未満の血小板減少症が認められる場合には，血小板濃厚液の投与を行う．血小板濃厚液には比較的新鮮な血漿成分が含まれている．したがって，血小板濃厚液投与を行った場合には，凝固因子のある程度の補充もできる．

抗血小板薬の投与を受けている患者で，血小板機能低下が強く疑われる場合には，血小板数が正常であっても血小板濃厚液を投与する必要がある．

(5) アルブミン製剤

循環血液量の50%以上の出血がある場合には，等張アルブミン製剤の投与を考慮する．ただし，重症患者においてアルブミン製剤による予後の改善には疑問がもたれており，必須な血液分画製剤とはいえない[2]．ヒドロキシエチルデンプン（HES）のような血漿増量剤で代用できる．

③ 大量輸血時の凝固異常

大量出血が起きた場合には，凝固因子や血小板の希釈性減少が起き，出血傾向が出現する（**図Ⅵ·B-1**）．低体温となると血小板凝集能が抑制されるために出血傾向が出現する．凝固因子活性は正常値の20～40%あれば，十分な止血能を期待できる（表Ⅵ·B-2[1]）．凝固因子活性がそれ以下となった場合には出血傾向が出現する．フィブリノゲン濃度の減少が比較的早く起こることが報告されている[3]．

また，高度の貧血自体で出血傾向が起こることが報告されている[4]．これは，血球が少なくなると血管中央部を流れやすくなり，血管損傷部に血栓ができにくくなるためと考えられる．

④ 大量輸血時の適合血の選択

(1) 赤血球製剤

輸血時の最大の安全性を目指すのであれば，交差適合試験を終えた輸血用血液を選択すべきである．しかし，交差適合試験を行うには少なくとも40分はかかる．急速な出血がある場合には，循環血液量や酸素運搬能を維持するために交差適合試験結果を待つだけの時間的余裕がない場合もある．

表Ⅵ・B-3　緊急輸血時の異型適合血

患者 ABO 血液型	異型適合血
O	なし
A	O
B	O
AB	A, B, O
未確定	O

交差適合試験の終了を待つ余裕がない場合には，型適合輸血を行う（**表Ⅵ・B-3**[1]）．定時手術において，タイプアンドスクリーン（T&S）が行われていれば，想定外の急速出血や出血量の増加があった場合には，あらかじめ T&S をすませておいた輸血用血液とのコンピュータクロスマッチを行ったり，生理食塩液法で血液型を確認した後に輸血を行う．型適合血さえも入手できない場合には，O 型血を含め，異型適合血の輸血を行う．

日本麻酔科学会による麻酔科認定病院を対象とした調査では，術前からの出血性ショックがあった場合，交差適合試験が省略されたのは 16.4%，O 型血の輸血が行われたのは 2.1%，術中大量出血の場合は，それぞれ 10.9%，0.6%と報告されている[5]．

不規則抗体が存在する場合があり，遅発性の溶血反応が起こりうる[6]．交差適合試験を省略して輸血した場合でも，交差適合試験は実施し，事後に不適合血であったと判明した場合には，その後の溶血反応を含めた輸血反応に注意する必要がある．

日本人における Rh 陰性の頻度は 0.5%程度である．Rh 陰性の患者に緊急輸血を行う場合には，Rh 陰性の輸血用血液の入手に努めるが，Rh 陽性の輸血用血液の輸血も可能である．とくに女児や妊娠可能な女性では，できるだけ早期に Rh 陰性の輸血用血液に切り替えるようにする．また，術後 48 時間に不規則抗体検査を実施し，抗 D 抗体が検出されない場合には，抗 D 免疫グロブリンの投与を考慮する．

(2) 新鮮凍結血漿

原則として ABO 同型製剤を使用する．A 型や B 型の患者に対しては，AB 型の新鮮凍結血漿も使用できる．O 型の患者に対しては，すべての血液型の新鮮凍結血漿が使用できる[7]．

(3) 血小板濃厚液

原則として ABO 同型製剤を使用する．同型製剤が準備できない場合には，AB 型血小板か，洗浄 O 型血小板を使用すべきである．

5 大量輸血時の合併症

大量出血時には，以下のような合併症が起こりうる．

① 低カリウム血症：代謝性アルカローシスなどが起こると，血漿カリウムが細胞内に移行して低カリウム血症となることがある．大量輸血が終わり，しばらくして出現しやすい．

② 高カリウム血症：赤血球濃厚液は，保存期間が長くなると上清カリウム濃度が上昇する（**表Ⅴ・B-4**）．とくに放射線照射を行った赤血球濃厚液においては，上清カリウム濃度が上昇する．保存後 21 日では 50 ～ 60mEq まで上昇する．上清の量は少なく，カリウム量としては，400ml 由来の MAP 加赤血球濃厚液で 6 ～ 7mEq と多くないが，大量輸血では高カリウム血症が起こりうる．最近使用されている加圧により急速輸血が可能な加温システム（レベル 1[8]

表Ⅵ・B-4　照射赤血球M・A・P「日赤」の含有成分の経時的変化
(400ml採血由来，採血後2日目に照射)

2日目	照射直後	7日目	14日目	21日目
照射なしの場合の上清カリウム(mEq/l)	3.8±0.3(照射直後)	32.1±2.1	48.8±2.5	58.6±2.7
照射した場合の上清カリウム(mEq/l)	4.1±0.4	16.7±1.1	21.7±1.5	27.9±1.7
pH	6.4±2.2	6.76±0.03	6.69±0.03	6.67±0.04
2,3-DPG (μmol/gHb)	6.80±0.03	0.5±0.2	0.3±0.1	0.4±0.1

(厚生労働省[1]；P68より改変)

など）や，輸血ポンプを使用すると，短時間内に大量輸血が可能となり高カリウム血症が起こる可能性がある[8]．1.2ml/kg/分以上の輸血速度では高カリウム血症が起こりうる．代謝性アシドーシスや呼吸性アシドーシスなど細胞内からのカリウムの細胞外移行を助長するような因子があると，高カリウム血症が起こりやすくなる．また，新生児や，腎機能低下患者でカリウム排泄が障害されている場合にはとくに注意を要する．

高度の高カリウム血症は心停止の原因となる．

③ **低カルシウム血症**：赤血球濃厚液の保存液には，カルシウムイオンをキレート化して取り除くためにクエン酸が含まれている．また，新鮮凍結血漿にもクエン酸が含まれている．そのため，赤血球濃厚液や新鮮凍結血漿の急速投与により大量のクエン酸が循環血液のなかに入るために，低カルシウム血症が起こりうる．そのために，低血圧，さらには心停止も起こりうる．

④ **代謝性アシドーシス**：赤血球濃厚液の保存中には，血球の代謝により有機酸が産生される．急速大量輸血を行った場合には，それらの酸により代謝性アシドーシスが起こる可能性がある．アシドーシスと低体温は出血傾向を助長する可能性がある[9]．

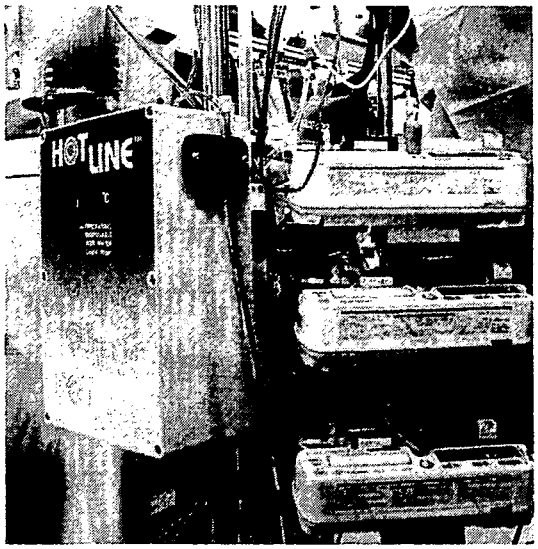
⑤ **代謝性アルカローシス**：クエン酸が代謝されることにより重炭酸ができ，代謝性アルカローシスとなる．

⑥ **希釈性凝固障害**：前述したとおり，循環血液量を超えるような出血に対して輸液やMAP加赤血球濃厚液の投与のみを行った場合には，希釈性凝固障害が起きうる．

⑦ **希釈性血小板減少症**：前述したとおり，循環血液量を超えるような出血に対して，輸液やMAP加赤血球濃厚液の投与のみを行った場合には，希釈性凝固障害が起きうる．

⑧ **低体温**：血小板濃厚液は室温保存であるが，赤血球濃厚液は2～6℃程度で保存されている．新鮮凍結血漿も融解後の温度も低い場合が多い．したがって，血液製剤を急速投与すると，低体温が起こりうる．低体温は血小板機能抑制や血管反応性低下を起こして出血傾向を助長し，出血量を増加させる[10]．輸液・輸血加温器を用いて輸血を行う必要がある．最近は，ホットライン®やレンジャー®など加温効率のよい輸液・輸血加温器が市販されている（**図Ⅵ・D-3**）．

⑨ **肺機能異常—輸血関連急性肺障害**：輸血関連急性肺障害transfusion-related acute lung injury（TRALI）は，最近注目されるようになった輸血合併症である．頻度は高くない（0.1%未満）が，死亡にいたる重症例（死亡率は5～20%）も存在する．輸血後6時間以内に発症する．寒気，発熱，呼吸困難，喀痰を伴わない咳，低血圧，低酸素血症などが起こる．胸部エックス線の写真上では，多数の結節と下肺野に浸潤影を認め，心拡大や肺血管陰影の



(厚生労働省編：血液製剤の使用にあたって，第3版，じほう社，2005，p.40)[1]

図Ⅵ・B-3　出血に伴う血液成分の変化と輸液・輸血製剤の基本

増強がないことなどが特徴的である．これらの症状は48時間から96時間以内に改善・消失する．全血製剤や，新鮮凍結血漿，血小板濃厚液など高力価の白血球抗体を含む血液製剤の使用で起こりやすい．ただし，MAP加赤血球濃厚液で起きた例も報告されている．

⑩　**酸素解離曲線のシフト**：輸血用血液はその保存中に2,3-ホスホグリセリン酸（DPG）が枯渇する．その結果，酸素解離曲線の左方シフトが起こる．そのため，Hbは組織で酸素を放出しにくくなる．輸血を行っても，組織酸素化の改善が起こるまでには2,3-DPGレベルが回復するまで数時間がかかるといわれている．しかし，最近の報告では，輸血により比較的速やかに組織酸素化が改善することが示唆されている[11]．

⑪　**ナトリウム負荷**：新鮮凍結血漿1単位には0.8g程度のNaClが含まれる．新鮮凍結血漿の大量投与によりナトリウム負荷が起こりうる．代謝性アシドーシスの治療に，炭酸水素ナトリウムを大量に投与した場合にも高ナトリウム血症が起こる．

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(稲田英一)

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Letter to the Editors-in-Chief

Pitavastatin attenuates the upregulation of tissue factor in restraint-stressed mice

To the Editor:

Hypercoagulability and thrombotic tendency are frequently induced by a variety of stressors. Indeed, the presence of psychosocial stressors has been associated with increased risk of acute myocardial infarction [1]. The restraint stress model often has been used to investigate the stress response experimentally in terms of pharmacologic, physiologic, or pathologic phenomena in vivo [2]. Tissue factor (TF) is a key procoagulant gene because it is the primary cellular initiator of the coagulation protease cascade and serves as a specific cofactor for plasma factors VII/VIIa [3]. We previously reported that a restraint (immobilization) stress, a typical physicopsychological stress, to mice induced the TF gene expression in several tissues, including kidneys and adipose tissues [4]. Statins, 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, have been broadly used for the prevention from cardiovascular diseases primarily with their lowering serum cholesterol levels. Statins also exert pleiotropic and beneficial effects on coagulation system, which are regarded to be independent of cholesterol lowering action. In particular, statins have been shown to reduce the TF expression in lipopolysaccharide-stimulated macrophages and smooth muscle cells in vitro, and in carotid lesions of cholesterol-fed rabbits in vivo [5,6].

We have observed that pitavastatin attenuated the upregulation of TF gene in restraint-stressed mice. Eight-week-old male C57BL/6J mice were administrated with 10 mg/kg/day of pitavastatin or atorvastatin for 3 weeks before the animals received restraint stress. Restraint stress, RNA extraction and RT-PCR assay were performed, as described previously [4]. All procedures were carried out according to the protocol approved by the Animal Care and Use Committee of Nagoya University. Twenty hours of restraint stress to mice caused a substantial induction of TF mRNA in the kidney and adipose tissues [4], which has been regarded to be a major source of TF [7]. Pitavastatin attenuated the induction of TF mRNA by stress in these tissues in about 50% of the control (i.e., statin free) mice, while atorvastatin did not (Fig. 1). As plasma cholesterol levels were not affected by statins in these mice (not shown), pitavastatin could suppress the upregulation of TF gene independently of cholesterol lowering action in restraint-stressed

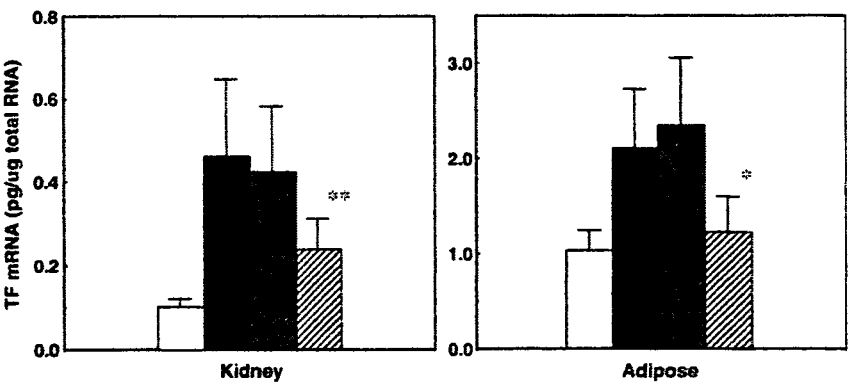

Figure 1 Eight-week-old mice had been administered with pitavastatin (10 mg/kg/day) or atorvastatin (10 mg/kg/day) for 3 weeks ($n=6$, respectively), followed by 20-h restraint stress. As a control group, we prepared non-stressed mice and 20-h-stressed mice without statin therapy ($n=6$, respectively). Kidneys and adipose tissues were harvested and analyzed for TF mRNA by quantitative RT-PCR. White bars: no restraint stress; black bars: only 20-h restraint stress; dark gray bars: pre-treatment with atorvastatin followed by 20-h restraint stress; hatched bars: pre-treatment with pitavastatin followed by 20-h restraint stress. $^{*}p<0.05$; $^{**}p<0.04$.

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mice. The inhibition of HMG-CoA reductase by statins leads to the decreased synthesis of cholesterol and its associated precursors, which are isoprenoid products (e.g., geranylgeranylpyrophosphates) from mevalonate. It has also been reported that statins reduces the TF expression by suppressing the formation of a geranylgeranylated proteins required for the proper synthesis of TF [8]. Thus, pitavastatin could attenuate the TF induction in restraint-stressed mice through the inhibition of geranylgeranylated protein synthesis.

Several differences are observed in pleiotropic effects between statins. Although there have been some reports on the inhibitory effect of atorvastatin on the TF expression in vitro or ex vivo [9,10], its suppressive effect in vivo is still controversial [11,12]. Restraint stress induces inflammatory cytokines (e.g., TNF-α) [4] and oxidative stress markers (e.g., 4-hydroxynonenal and 8-hydroxy-2′-deoxyguanosine) [13], both of which could upregulate TF gene expression in vivo [4,14]. In this context, statins inhibit TNF-α-induced nuclear factor κB (NF-κB) activation [15], which stimulates the TF expression, although they differ in their ability to block NF-κB activation [16]. Pitavastatin could strongly suppress the molecular responses against stress insults, which include the induction of cytokine-induced NF-κB and the production of oxidative stress markers in the ischemic model in vivo in comparison with atorvastatin [17]. Taken together, pitavastatin would attenuate the TF expression induced by stress through the inhibition of TNF-α-induced NF-κB activation (i.e., anti-inflammatory) and its anti-oxidative effect. The finding in this study suggests that pitavastatin contributes to the prevention from thrombotic cardiovascular diseases associated with physicopsychological stress although additional studies to elucidate its mechanism are required.

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Review Article

Intravenous Immunoglobulin Therapy for Acquired Coagulation Inhibitors: A Critical Review

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Abstract

Intravenous immunoglobulin (IVIG) therapy has been used for autoimmune diseases and disorders involving autoantibodies, including coagulation inhibitors. In this review, we have evaluated the efficacy and safety of IVIG therapy for acquired coagulation inhibitors, including factor VIII inhibitor, and for acquired von Willebrand syndrome on the basis of 44 reports published between 1965 and 2005. Among 35 patients with factor VIII inhibitor, we estimated the efficacy of IVIG therapy alone (which includes complete remissions and partial responses with a clinical benefit) to be 30% (11 cases), whereas the response to combination therapy with IVIG plus immunosuppressive agents (eg, corticosteroid, cyclophosphamide) seemed to be better (approximately 70%, 33/45 cases) than with IVIG therapy alone. In acquired von Willebrand syndrome, the efficacy of IVIG therapy was estimated to be 30%. The response to IVIG therapy appears to occur rapidly, and coagulation inhibitors seem to be neutralized immediately. Moreover, severe complications or side effects rarely occur during IVIG treatment. IVIG therapy thus may be considered one choice for treating acquired coagulation inhibitors, although its efficacy improves when used in combination with immunosuppressive agents.
Int J Hematol. 2007;85:287-293. doi: 10.1532/IJH97.06222

Key words: Intravenous immunoglobulin therapy; Acquired coagulation inhibitors; Autoimmune disease; Factor VIII inhibitor; von Willebrand syndrome

1. Introduction

Intravenous immunoglobulin (IVIG), a highly purified immunoglobulin G (IgG) fraction derived from pooled human plasma, is currently one of the most widely used plasma components in the world [1,2]. It was originally introduced as replacement therapy for patients with primary immunodeficiency disorders. In 1981, Imbach et al reported a serendipitous observation that a high-dose infusion of IVIG (2 g/kg of body weight infused over 5 days) was able to transiently increase the platelet count in children with idiopathic thrombocytopenic purpura (ITP) [3]. With the encouragement of this and other reports on ITP [4], the clinical applications of IVIG have increased markedly over the past 25 years to include many autoimmune diseases. IVIG has been shown to be efficacious in clinical trials for graft-versus-host disease [5], myasthenia gravis [6], Guillain-Barré syndrome [7], Kawasaki disease [8], and chronic inflammatory demyelinating polyneuropathy [9]. It has also been used to treat immune neutropenia and coagulation inhibitors [10-12], but its efficacy and safety have not been firmly established.

Coagulation inhibitors, antibodies against individual clotting factors, interfere with blood coagulation. The most common coagulation inhibitor is factor VIII inhibitor, an antibody against factor VIII that neutralizes the coagulant activity of factor VIII. Factor VIII inhibitor develops in patients with hemophilia A as an alloantibody after replacement therapy or spontaneously as an autoantibody in nonhemophilic patients [13], including postpartum patients and those with autoimmune disease, malignancy, or diabetes [14]. Once developed in such patients, factor VIII inhibitor poses a serious problem for the management of bleeding episodes, because any infused factor VIII will be rapidly neutralized and will not be available to induce hemostasis [15]. Although IVIG therapy has been used as one of the immunotherapies

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for eradicating coagulation inhibitors, such an indication is considered off label [2].

The aim of this review is to examine the efficacy and safety of IVIG therapy in patients with acquired inhibitors against factors VIII, IX, or V, and in patients with acquired von Willebrand disease. Cases with lupus anticoagulant were not included in this review. An electronic search of the Medline/PubMed database from 1965 to 2005 was performed to identify relevant articles. This search yielded 108 citations, 72 of which were considered appropriate and reviewed. The bibliography of each review paper was examined to identify articles that may have been missed by our electronic searches.

2. History

In 1983, Nilsson et al reported an interesting observation [11]. A patient with severe hemophilia B and factor IX inhibitor was treated with extracorporeal protein A–Sepharose adsorption to remove the inhibitor, followed by the administration of factor IX concentrate and cyclophosphamide. This procedure produced a 15-fold increase in factor IX inhibitor on one occasion but did not cause any increase of the inhibitor titer on another occasion, when 5 g of IVIG was also given to the patient to restore the reduced IgG level. The investigators suggested that the administration of IVIG appeared to suppress antibody synthesis in hemophilia B patients with factor IX inhibitor.

Three groups of investigators reported the use of IVIG in the management of factor VIII inhibitors in 1984 [12,16,17]. IVIG therapy combined with vincristine produced a transient disappearance of acquired factor VIII inhibitor along with a slow rise of factor VIII activity in a 13-year-old boy with autoimmune disease [16]. IVIG therapy was ineffective in 2 patients with hemophilia A inhibitor [17]. Sultan et al [12] reported that IVIG therapy (0.4 g/kg body weight per day for 5 days) resulted in the rapid, marked, and prolonged suppression of factor VIII inhibitor in 2 patients with acquired factor VIII antibody (autoantibody) but that it had little or no effect in 2 hemophilic patients with factor VIII antibody (alloantibody). They showed by in vitro experiments that IVIG preparations were able to neutralize the anti–factor VIII activity of the patients' plasma and the IgG fraction of the patients' sera. Many articles were subsequently published on the effect of IVIG on acquired factor VIII inhibitors, as is discussed later.

3. Possible Mechanisms of Action

The rapid rise in the platelet count in ITP following IVIG administration is thought to occur through binding to and blocking Fcγ receptors on macrophages, thereby preventing the removal of antibody-coated platelets by the reticuloendothelial system in the spleen and liver [4]. This mechanism, however, does not appear to explain the effect on coagulation inhibitors.

Several hypotheses on the mechanisms of action of IVIG on factor VIII inhibitor have been put forward. Sultan et al and Kazatchkine and Kaveri postulated that anti-idiotypic antibodies present in IVIG preparations neutralize factor VIII autoantibodies [12,18]. $F(ab')_2$ fragments from IVIG preparations inhibited anti–factor VIII activity in $F(ab')_2$ fragments from the patient's plasma. Anti–factor VIII $F(ab')_2$ fragments were specifically retained on an affinity column of Sepharose-bound $F(ab')_2$ from IVIG, indicating that a direct interaction occurred through the antibody-binding sites of both immunoglobulins [19]. Anti-idiotypes against various autoantibodies were shown to be present in pooled normal human polyspecific immunoglobulin. In addition, IgG prepared from elderly donors and multiparous women was reported to contain a higher frequency of neutralizing antibodies against factor VIII autoantibodies [20]. It is puzzling that such an in vitro antibody-neutralizing effect was not always demonstrated, even though in vivo administration of IVIG produced a marked reduction of the inhibitor titer [21,22].

The fall in inhibitor titer following IVIG therapy without simultaneous immunosuppressive treatment appears to be rapid (within several days) in most cases [12,23,24] but is slow (more than 10 days) in others [22,25]. There must be slow effects of IVIG on autoantibody production. In addition to its direct and immediate action on antibodies, IVIG has been proposed to suppress antibody formation by B-cells, a process mediated through the down-regulation of Fcγ receptors [26]. Furthermore, IVIG may induce T-cell suppressor activity [27]. These observations taken together suggest that IVIG exerts its effect on the inhibitor titer through more than one mode of action.

4. Efficacy

4.1. Factor VIII Inhibitor

We extensively reviewed the international literature published from 1965 to 2005. The typical IVIG dosage used for treating factor VIII inhibitor was 0.4 g/kg per day for 5 consecutive days.

The efficacy criteria (ie, the response to IVIG therapy) were as follows [28]: Complete remission (CR) was defined as the disappearance of the inhibitor, partial response (PR) was defined as a decrease in the inhibitor titer by at least 25% of the baseline value, and failure was defined as other than CR and PR.

In Table 1, we present all of the cases in which the efficacy of IVIG treatment alone was evaluated [12,22-25,28-40]. The response to IVIG therapy alone was failure in 11 cases (31.4%) and PR in 21 cases (60.0%), but with a subsequent clinical benefit in only 8 patients. Finally, 3 patients (8.6%) achieved CR. The efficacy of IVIG therapy alone, which includes CR and PR with a clinical benefit, among these 35 patients was estimated to be 31.4% (11 cases). In most cases of CR or PR, the response to IVIG treatment was rapid, and factor VIII inhibitor seemed to be neutralized immediately.

We summarize the responses to combined therapy with IVIG plus immunosuppressive agents in Table 2 [21,25, 28,32,35,38-52]. The response to IVIG plus steroid and/or cyclophosphamide therapy was better than to IVIG treatment alone. CR was achieved in 19 (73%) of 26 patients who were treated with IVIG plus steroid. In addition, 14 (74%) of 19 patients who received IVIG plus steroid and

Table 1.
Evaluable Patients from the Literature with Acquired Factor VIII Inhibitor Who Were Treated with Intravenous Immunoglobulin (IVIG)*

No.	Reference	Sex/Age, y	Associated Disease	IVIG Dosage, g/kg per d	Inhibitor Titer, Bethesda U		Response	Clinical Outcome
					Before	Nadir (d†)		
1	Hudak et al [29]	F/40	Postpartum	0.5 × 5 d	16	<1 (105)	CR	Sustained remission
2	Schwartz et al [25]	M/68	CLL	1 × 2 d	1	0 (14)	CR	Sustained remission
3	Schwartz et al [25]	F/83	Diabetes	1 × 2 d	0.9	0 (61)	CR	Sustained remission
4	Sultan et al [12]	M/62	Idiopathic	0.4 × 5 d	25,000	550 (3)	PR	No clinical benefit‡
5	Sultan et al [12]	F/29	Postpartum	0.4 × 5 d	10,500	1000 (3)	PR	No clinical benefit
6	Zimmermann et al [30]	F/64	Idiopathic	0.5 × 8 d	75	10 (25)	PR	Clinical benefit
7	Zimmermann et al [30]	F/70	Idiopathic	0.5 × 8 d	51	3.8 (9)	PR	Clinical benefit
8	Newland et al [22]	F/71	Diabetes	0.4 × 5 d	50	20 (45)	PR	Clinical benefit
9	Heyman et al [31]	M/64	Idiopathic	0.4 × 5 d	47	28 (17)	PR	No clinical benefit
10	Nishida et al [23]	F/39	Idiopathic	0.4 × 5d	115	17 (3)	PR	No clinical benefit
11	Schwerdtfeger et al [32]	F/31	Postpartum	0.5 × 5 d	420	104 (6)	PR	No clinical benefit
12	Sultan et al [33]	M/78	NA	0.4 × 5 d	42	20 (30)	PR	No clinical benefit
13	Sultan et al [33]	M/72	Carcinoma	0.4 × 5 d	38	10 (5)	PR	Transient benefit
14	Schwartz et al [25]	M/54	Alcoholism	1 × 2 d	1228	208 (7)	PR	No clinical benefit
15	Schwartz et al [25]	F/72	Idiopathic	1 × 2 d	880	570 (48)	PR	No clinical benefit
16	Schwartz et al [25]	F/25	Idiopathic	1 × 2 d	280	1.9 (57)	PR	Clinical benefit
17	Schwartz et al [25]	F/38	Postpartum	1 × 2 d	102	56 (22)	PR	Clinical benefit
18	Schwartz et al [25]	M/77	Carcinoma	0.4 × 5 d	39	24 (3)	PR	No clinical benefit
19	Schwartz et al [25]	M/60	Griseofulvin	0.4 × 5 d	29	18 (19)	PR	No clinical benefit
20	Crenier et al [28]	M/65	Cardiomyopathy	0.4 × 5 d	120	72 (30)	PR	No clinical benefit
21	Crenier et al [28]	M/74	Bronchitis	0.4 × 5 d	24	12 (7)	PR	No clinical benefit
22	Michiels et al [24]	F/31	Postpartum	0.5 × 5 d	12	1 (11)	PR	Clinical benefit
23	Lafferty et al [34]	F/42	SLE	0.4 × 5 d	500	185 (NA)	PR	Clinical benefit
24	Walsh et al [35]	F/72	Cholecystitis	30 g × 1 d	6	NA	PR	Clinical benefit
25	Hiller et al [36]	M/57	Surgery	30 g × 5 d	24	20 (2)	F	Transient benefit
26	Casas et al [37]	M/70	Lymphoma	0.4 × 7 d	8.6	35 (NA)	F	Transient benefit
27	Sultan et al [33]	M/45	Vasculitis	0.4 × 5 d	25	28 (NA)	F	NA
28	Pignone et al [38]	F/66	RA	0.4 × 6 d	13	26 (7)	F	NA
29	Hauser et al [39]	F/29	Postpartum	0.4 × 5 d	10	110 (NA)	F	NA
30	Mateo et al [40]	F/82	CLL	0.4 × 5 d	9.5	10 (30)	F	NA
31	Schwartz et al [25]	M/64	Diabetes	1 × 2 d	452	340 (6)	F	No clinical benefit
32	Schwartz et al [25]	F/83	LA	0.4 × 5 d	102	96 (5)	F	No clinical benefit
33	Schwartz et al [25]	F/48	Idiopathic	1 × 2 d	59	46 (2)	F	No clinical benefit
34	Schwartz et al [25]	M/73	Carcinoma	0.4 × 5 d	42	108 (5)	F	No clinical benefit
35	Schwartz et al [25]	M/62	Idiopathic	1 × 2 d	1.4	1.4 (11)	F	No clinical benefit

*CR indicates complete remission; CLL, chronic lymphocytic leukemia; PR, partial response; NA, not available; SLE, systemic lupus erythematosus; F, treatment failure; RA, rheumatoid arthritis; LA, lupus anticoagulant.
†Number of days after starting IVIG treatment.
‡Subjective evaluation by the doctors in charge.

cyclophosphamide reached CR. Only 2 cases of treatment with IVIG plus cyclophosphamide were reported, and these patients achieved CR [52]. Conversely, 18 (75%) of 24 patients treated with steroid plus cyclophosphamide instead of IVIG achieved CR. This degree of efficacy is consistent with the report by Green et al [45]. In these reports, however, the evaluation of efficacy depended on the patients' symptoms (ie, improvement of bleeding tendency), because the disappearance of inhibitors was not followed up.

Thus, the overall efficacy of IVIG therapy alone is almost 30%, whereas that of a combination therapy with IVIG plus steroid and/or cyclophosphamide is approximately 70%.

Recent reports have described patients with acquired factor VIII inhibitors who rapidly responded to immunosuppressive regimens including rituximab, a monoclonal antibody against $CD20^+$ B-cells [53,54]. These data suggest that immunosuppressive therapy using rituximab could become a powerful tool against coagulation inhibitors.

4.2. Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome is a rare bleeding disorder with laboratory findings similar to those of congenital von Willebrand disease. According to an international registry, acquired von Willebrand syndrome is primarily associated with lymphoproliferative diseases, immunologic and cardiovascular disorders, and solid tumors. The prevalence of acquired von Willebrand syndrome in these underlying disorders is still unknown.

IVIG was also effective in stopping bleeding in acquired von Willebrand syndrome [55]. Several groups reported that acquired von Willebrand syndrome associated with systemic lupus erythematosus [56], monoclonal gammopathy [57-60], malignant lymphoma [61], and prostatomegaly [62], and of undefined origin [63,64] responded well to IVIG therapy. Some patients were successfully treated with the combination of IVIG and desmopressin, but the effect was transient

Table 2.
Responses of Patients with Acquired Factor VIII Inhibitor to Immunosuppressive Agents with or without Intravenous Immunoglobulin (IVIG) Therapy

	IVIG + Pr (26 Cases)			IVIG + Pr + Cy (19 Cases)			Pr + Cy (24 cases)		
Reference	CR	PR	F	CR	PR	F	CR	PR	F
Green et al [41]	1								
Carreras et al [21]	1*								
Heyman et al [31]			1†						
OiSullivan et al [42]					1				
Pirner et al [43]					1				
Lionett et al [44]	1								
Pignone et al [38]							1		
Green et al [45]							5		5
Hauser et al [39]							1		
Mateo et al [40]	1								
Schwartz et al [25]	1	1							
Crenier et al [28]	1			1					
Lafferty et al [34]					1				
Sohngen et al [46]							2		
Bossi et al [47]	4		1	8		1	3		
Gandini et al [48]	1								
Dykes et al [49]	4	1	2						
Grunewald et al [50]				2			4		
Mazzucconi et al [51]	3	1							
Delgado et al [52]	1			3	1		2		1
Total	19	3	4	14	4	1	18		6

*Pr indicates prednisolone or dexamethasone; Cy, cyclophosphamide; CR, complete remission; PR, partial response; F, treatment failure.

†IVIG dosage: 0.4 g/kg per d for 2 d.

in most cases. According to data from an international registry, the efficacy of IVIG therapy in acquired von Willebrand syndrome was estimated to be 30% (21/63 patients) [65,66]. Of note, however, is that in most cases the efficacy of IVIG was subjectively evaluated (ie, a good response means to stop bleeding) by the doctors in charge. This efficacy is similar to that for treatment with desmopressin (38/119) or with immunosuppressive agents (23/66), but corticosteroids alone were effective in only 19% of patients (12/63).

4.3. Other Coagulation Inhibitors (Factor V or IX Inhibitor)

Patients with inhibitors against factor V or IX are extremely rare. Only one report described acquired factor IX inhibitor developing in a patient with autoimmune polymyositis [67]. Single-agent therapy with IVIG was effective in suppressing inhibitor synthesis and in stopping bleeding. Another report described acquired factor V inhibitor developing in an 82-year-old female patient following abdominal surgery [68]. Nine-day treatment with IVIG (0.4 g/kg per day) was partially effective in suppressing the inhibitor titer and improving the patient's hemorrhagic diathesis.

5. Safety

Adverse reactions to IVIG therapy are usually mild and self-limited: headache, back pain, low-grade fever, myalgia, and chills. The IVIG preparations currently in clinical use are also assumed to carry virtually no risk of transmitting infectious agents. Rarely, however, serious complications can occur. In recent years, thromboembolic complications have occasionally been reported in patients who received IVIG. Stroke, acute myocardial infarction, and deep vein thrombosis were estimated to occur at an incidence of 3% to 5% [69]. Thromboembolism appeared to develop mainly in patients who had other risk factors, such as an advanced age, being bedridden, and a history of thromboembolism. What triggers thromboembolic complications? During 5 courses of treatment with IVIG (24-54 g/day), the plasma IgG concentration was noted to increase 4-fold, and plasma viscosity increased to beyond the normal range [70]. It appears that increased blood viscosity after high-dose IVIG infusion is responsible for thromboembolism. Slow infusion of IVIG (a daily dose of 0.4 g/kg in not less than 8 hours) has been recommended to prevent thromboembolism [71].

Interestingly, our own review of the literature revealed no thromboembolic complications in 80 patients with acquired factor VIII inhibitor who had received IVIG. It is tempting to speculate that the presence of a coagulation inhibitor may counteract thrombosis formation.

6. Discussion

In general, treatments of acquired coagulation inhibitors are divided into 2 approaches: One is to stop the present bleeding events, and the other is to remove inhibitors by immunomodulative therapy. In cases of acute bleeding in patients with factor VIII inhibitors, conventional management consists of human factor VIII concentrate or desmopressin for low inhibitor levels (<5 Bethesda U) and porcine factor VIII or bypass therapy (eg, recombinant activated