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The perils of proxy outcomes in evidence-based medicine: the case of recombinant Factor VIIa

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Abstract

There is currently a major controversy surrounding the off-label use of recombinant activated Factor VII (rFVIIa). The literature offers at best inconclusive support for its use in the management of bleeding in any situation other than in patients with Factor VII deficiency or hemophilia A or B with antibodies to factor VIII or factor IX respectively. This evidence has not, however, slowed the growth in off-label prescribing of rFVIIa in other situations including intracranial hemorrhage, cardiac surgery, trauma, transplantation and prostatectomy. We argue that the controversy surrounding such off-label use of rFVIIa stems in part from different understandings of the purposes and methods of evidence-based medicine (EBM) - in particular the use of gross, proxy outcomes such as mortality to determine the effectiveness of an intervention. We then argue that clinical impression and expert opinion should not be dismissed outright on the basis of inconclusive evidence of ineffectiveness. Those who advocate its continued use, however, have a responsibility to demonstrate the benefits that may be missed in current manifestations of EBM. We suggest that the only justified verdict in the case of rFVIIa is currently 'Not Proven'.

Keywords

Clinical experience, evidence, evidence-based medicine, outcomes, proxy outcomes, recombinant Factor VIIa

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Introduction

Readers of general medical journals will have recently seen a series of articles, editorials and letters in a number of prominent publications arguing the pros and cons of the 'off-label' use of recombinant Factor VIIa (rFVIIa) for the treatment of major hemorrhage [1-5]. There is compelling evidence to support the use of rFVIIa for the control of bleeding in very rare cases of Factor VII deficiency and in the rare cases of hemophilia with inhibitors to Factor VIII or IX. For these uses, it has FDA approval. Because of the role that Factor VII has in normal hemostasis and thrombosis, it has also been used in bleeding associated with obstetrics [6], cerebral trauma [7] and other causes of

intracranial haematoma, cardiac surgery [8], urology [9] and general trauma [10]. This logic has led clinicians to an enormous increase (over 140-fold) in off-label prescribing of rFVIIa in less than a decade, to the extent that 97% of its use is now 'off-label' [5]. Clinicians who prescribe rFVIIa off label probably do so for good reason. There is a clear physiological mechanism that would suggest that rFVIIa would work in any of these contexts. rFVIIa has also been seen to 'work' in bleeding patients and there is some evidence from controlled studies that rFVIIa can reduce hematoma expansion and transfusion requirements in some contexts, such as warfarin-associated intracranial bleeding [11] and prostatectomy [9].

Evidence-based Medicine

Enter epidemiology and evidence-based medicine (EBM). A recent systematic review by Yank et al [4] suggests rFVIIa has no benefit (in terms of reduced mortality) in intracerebral hemorrhage, adult cardiac surgery or thoraco-abdominal trauma and that there may be an increased risk of thromboembolism (TE) when it is used to treat intracerebral hemorrhage and bleeding in adult cardiac surgery. While this review demonstrated some possible benefits, (including reduced hematoma expansion in cerebral hemorrhage and reduced adult respiratory distress syndrome in trauma), the strength of evidence was low for most positive outcomes and could have been accounted for (at least in part) by publication bias arising from the fact that most trials were sponsored by the manufacturer of rFVII, Novo Nordisk.

The accompanying editorial in the *Annals of Internal Medicine* used the results of the systematic review to condemn the off-label use of rFVIIa and raised the possibility of legal action against “physicians who persist in such use in the face of clear evidence of inutility and harm (and who) could be subject to civil action by the affected patients or their heirs” [2]. Unsurprisingly, the review and editorial generated heated responses suggesting that clinical demands and impressions would (and should) trump the evidence offered and that clinicians would (and should) continue to use rFVIIa for off-label indications [1,3]. The editors responded [2] that clinicians should ‘rise above the “availability heuristic” – the tendency to base decisions on the events which are most apparent at the time (diminution of bleeding) rather than on more complete risk-benefit information.’

The dispute has hallmarks of what the Harvard Business School might distinguish as ‘an EBM classic’ [12], a paradigm confrontation between the ‘hard’ and ‘soft’ extremes of EBM. At the hard end are those who insist that the evidence from a systematic review should trump clinical experience. At the other end stand clinicians who point out that “even if the safety data from existing randomized trials do apply...this risk is likely dwarfed by the risk of allowing blood loss to continue unabated...All procoagulant agents have the risk for potential adverse responses, but their individualized risk-benefit profile is largely dependant on the clinical context” [1]. So how can we progress this debate? In order to do so, we need to consider the purposes and methods of EBM.

EBM deals with outcomes and meta-analyses and collective reviews tend to deal with aggregated outcomes. While this provides a means for making gross assessments of the therapeutic efficacy of the intervention - the limits of this approach become clear in the dispute surrounding the off-label use of rFVIIa. Some argue that the (proxy) outcome of overall mortality should be the principal measure upon which the assessment of the effectiveness of rFVIIa should be based and should be the thing that guides

practice, while others are more concerned about the immediate clinical effect of rFVIIa - its effect on bleeding.

Intent and proxy outcomes

It thus becomes clear that the influence of intent is important in the debate about rFVIIa. What does the clinician intend to do at the moment of treatment? What does he hope to achieve? In the context of acute bleeding, it could be argued that he intends primarily to stop bleeding. Whether the patient subsequently then survives will depend not simply on the use of rFVIIa, but also on co-morbidities related either to the original insult or to the effects of hypotension or shock resulting from blood loss. According to this view, rFVIIa is only ineffective if it does not control bleeding. Mortality, therefore, may not be an adequate measure of the effectiveness of this, or any other, hemostatic agent.

This raises questions regarding the use of proxies in clinical research and practice. A proxy is a person or thing used to represent someone or something else for a particular purpose. We often choose outcomes in clinical trials, meta-analyses and collective reviews that are proxies for the effectiveness of interventions. This means that we sometimes use clear and simply measurable outcomes such as mortality to tell us whether a particular intervention is effective, often without regard for the purpose of the intervention. The problem with the use of such proxies is that subtle variations of intent can be missed by using evidence in this way. Death may follow urgent surgery for trauma, but the death might result from many causes including infection, prolonged hypotension before the surgery, renal failure and may not be an indicator that the surgery itself has failed [13]. While this intervention may be assessed in terms of its gross outcome (mortality), its intent (e.g. controlling acute bleeding) may be missed.

A way forward

So what is the way forward? How do we mediate between those concerned with the use of epidemiological outcomes as a guide to practice and those more concerned with immediate clinical outcomes such as reduced bleeding?

To resolve this, it might be helpful to bear in mind that we are faced with what have been called ‘essentially contested concepts’ [14]. Both sides sincerely believe they are right and they both have reasons to believe their rightness. They are seriously committed to their beliefs and there is an element of outrage in the arguments on both sides, one invoking legal sanction against the other [2], the other responding by invoking clinical obligations and necessities [1].

Many of us are conditioned by the tenets of evidence-based medicine to accept EBM findings and reject anything based on clinical impression. But both evidence-based medicine and the evidence of clinical observation have a place in medicine. Neither of these can be

uncontroversially privileged. We consistently rely upon the combined and long-enduring experience of generations of medical practitioners, but we also accept that we should apply the 'best available' evidence, even if its outcomes may not be directly relevant to the question at hand [15]. The fact that both sides 'know' that they are right with equal conviction shows that neither those advocating the use of rFVIIa, nor those condemning it, have access to the 'truth'. There needs to be a balance between clinical observation and scientific evidence. Neither have all the answers for so complex a praxis as medicine.

In this case, therefore, rather than condemning those who prescribe rFVIIa off-label, we should demand further evidence to support or refute their practice. Are there certain patients in whom rFVIIa significantly reduces bleeding, or are these false impressions encouraged by wishful-thinking at critical moments and by the use of flawed proxies for blood loss (such as transfusion requirements and hematoma expansion)? And are there subtle, but clinically significant, measures of control that collective reviews and meta-analyses inevitably miss?

Conclusion

When clinical observation and scientific knowing come into conflict, as they do with the use of rFVIIa, science needs to ask "Are we missing something? How could we sensitise our investigations to the intuitions of practitioners?" The Scottish legal verdict of Not Proven is wise in agreeing that no other verdict is possible at this moment, but that a re-trial would be possible, should new evidence emerge. The verdict in the case of rVIIa surely remains Not Proven.

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