

CHANGE PAGE

Administer tranexamic acid early to injured patients at risk of substantial bleeding

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Change Page aims to alert clinicians to the immediate need for a change in practice to make it consistent with current evidence. We welcome any suggestions for future articles (change@bmj.com).

Haemorrhage is the principal cause of 30-40% of all trauma deaths, and half of these occur before admission to hospital.¹ Many bleeding patients develop coagulopathy, making control of haemorrhage more difficult. In some patients this coagulopathy develops early² and seems to be associated with excessive fibrinolysis and breakdown of clots.³ Current protocols for massive transfusions of blood products (variably defined as >10 red cell units or >50% blood volume in 24 hours, or >5 units in four hours) to patients with haemorrhagic shock prescribe plasma and cryoprecipitate to replace lost, consumed, diluted, or dysfunctional clotting factors, but these do not specifically treat fibrinolysis. There is now compelling evidence that tranexamic acid (1 g loading dose plus 1 g over eight hours), a relatively safe and inexpensive antifibrinolytic, should be administered within three hours of injury in patients at risk of severe bleeding.

The evidence for change

Tranexamic acid was discovered in the 1950s and has been used during surgery to minimise blood loss. A systematic review evaluated 126 randomised controlled trials in elective surgery and three in emergency surgery (total of 10 488 patients) that had been conducted between 1972 and 2011. This showed that tranexamic acid reduced blood transfusions by a third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65),⁴ an effect that persisted when only trials with adequate allocation concealment were considered (0.68, 0.62 to 0.74). In these higher quality trials the effect on mortality was uncertain (0.67, 0.33 to 1.34), as was the effect on myocardial infarction, stroke, and venous thromboembolism.

Tranexamic acid seems to work by inhibiting lysine binding sites on plasminogen, preventing its conversion to plasmin. Plasmin has potential fibrinolytic, inflammatory, and neurotoxic effects. The observed reduction in bleeding probably results from reduced fibrinolysis and therefore reduced clot breakdown. Like surgery, severe trauma and haemorrhage can accelerate fibrinolysis,³ which contributes to acute traumatic coagulopathy.²

In a systematic review of antifibrinolytic drugs in trauma⁵ the only trial to assess haemorrhage was the randomised placebo controlled CRASH-2 trial, which evaluated the effects of tranexamic acid in 20 211 adult trauma patients with or at risk of bleeding in 274 hospitals in 40 countries.⁶

METHODS

We searched the Cochrane Library and Medline for recent systematic reviews on the effects of tranexamic acid in trauma. For high quality reviews we repeated their search strategies to detect any primary studies published since the review. We also considered the potential relevance to trauma patients of the findings of a recent meta-analysis of tranexamic acid in elective surgery.

Tranexamic acid given within eight hours of injury reduced all cause mortality from 16.0% to 14.5% (relative risk 0.91, 95% confidence 0.85 to 0.97), and the risk of death resulting from bleeding from 5.7% to 4.9% (0.85, 0.76 to 0.96).⁶ There did not seem to be more vascular occlusive events, nor did the effect of tranexamic acid seem to vary by baseline risk of death.⁷ Subsequent re-examination of the 1063/3076 (35%) deaths that resulted from bleeding found that the benefit of tranexamic acid was greatest when given early (<1h: 0.68, 0.57 to 0.82; 1-3 h: 0.79, 0.64 to 0.97) and that, when given more than three hours after injury, an unexpected increase in deaths from bleeding was observed (1.44, 1.12 to 1.84).⁸ Extrapolation of the CRASH-2 data led to estimates that more than 100 000 in-hospital deaths globally could be averted annually⁹ and 315 to 755 life years saved per 1000 trauma patients, at a cost of \$45-\$64 (£28-£40; €35-€49) per life year saved.¹⁰

Military doctors were concerned that many of the patients in the CRASH-2 trial did not resemble their severely injured patients from the battlefield because only half the patients in the CRASH-2 trial needed a blood transfusion or needed surgery yet a comparatively high proportion (compared with battlefield patients) of them died. This concern led to an observational study of 896 patients wounded in Afghanistan, which found tranexamic acid was associated with higher survival and less coagulopathy.¹¹

Barriers to change

The largest barrier to change in trauma management is its incorporation into prominent guidelines on trauma management. Since the introduction of courses on advanced trauma life support in 1976, clinicians have realised the benefit of protocols for trauma management. Tranexamic acid has recently been included in the British armed forces guidelines (*Clinical Guidelines for Operations*) and the US military guidelines (*Joint Theater Trauma System*), and its use is reported to have greatly increased, although no data have been published. Adding tranexamic acid to civilian guidelines on advanced trauma life support and to other civilian guidelines would be expected to have a similar effect.

Some clinicians may wonder whether a single trial can provide definitive evidence for practice change in trauma, bearing in mind that the results of single trials are not always upheld in subsequent studies.¹² For example, the

KEY POINTS

Give tranexamic acid to trauma patients at risk of major haemorrhage as early as possible, but not at all if three hours have passed since injury
Incorporate tranexamic acid into protocols for prehospital trauma care where feasible
Seek further evidence, including mechanistic studies and confirmatory trials of benefits and potential harms in advanced trauma systems

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Previous articles in this series

- Don't use aspirin for primary prevention of cardiovascular disease (*BMJ* 2010;340:c1805)
- Advise use of rear facing child car seats for children under 4 years old (*BMJ* 2009;338:b1994)
- Consider β blockers for patients with heart failure (*BMJ* 2009;338:b1728)
- Prescribe systemic corticosteroids in acute asthma (*BMJ* 2009;338:b1234)
- Prescribe prednisolone alone for Bell's palsy diagnosed within 72 hours of symptom onset (*BMJ* 2009;338:b255)

conclusions of a recent large trial favouring the use of activated protein C in sepsis¹³ were reversed in subsequent studies. The consistent findings of the effects of tranexamic acid in 126 trials in elective surgery are somewhat reassuring in this regard.⁴

Another potential barrier to change is uncertainty about the generalisability of the CRASH-2 trial results to all trauma systems. Major trauma is different from elective surgery in that patients usually have multiple problems and survival depends on complex systems of care that co-ordinate access to necessary prehospital and hospital treatments. Pivotal to survival in haemorrhagic shock is a range of techniques for rapid control of bleeding, correction of coagulopathy, and critical care support. Countries that have invested heavily in trauma systems to coordinate and expedite access to time-critical care have reduced mortality substantially. Less than 2% of the patients in the CRASH-2 trial were treated in countries that are likely to have made such investments (such as Australia, New Zealand, North America, and western Europe).

Adding concern to the uncertainty about the balance of treatment benefits and harms in different settings is the unexplained increase in risk of death caused by bleeding when tranexamic acid was given more than three hours after injury. Plausible explanatory hypotheses, yet to be tested, include an adverse effect in established disseminated intravascular coagulation, development of a prothrombotic state, or a lack of effectiveness in patients in whom time had allowed hypothermia or acidosis to develop. Furthermore it is well established that major trauma elicits within minutes a widespread genomic response; affects the innate and adaptive immune systems; and causes systemic inflammation that can lead to multiple organ failure, sepsis, and death.¹⁴ The effects of tranexamic acid on these processes and on coagulation and fibrinolytic pathways, when administered at different times in the course of trauma resuscitation, have not been elucidated. If tranexamic acid has different effects at different administration times, other influences on coagulopathy (such as administration of clotting factor and platelets, temperature management, and timing of surgery) might also alter the balance of risk and benefit. The true incidence and associated harms of deep venous thrombosis and pulmonary embolus among CRASH-2 patients is unknown because most patients were not investigated with Doppler ultrasound scanning or computed tomography. Furthermore, many advanced trauma systems are used to treat patients who are older than most of those in the CRASH-2 trial. The interaction of tranexamic acid with age related comorbidities, pharmacotherapy, and risk of thrombotic complications in trauma is not fully understood.

Lack of certainty around these interactions and how they play out in different systems provides an opportunity to further investigate the effects of tranexamic acid on the biology of injury. However, concerns about external validity and limited understanding of mechanism in trauma should not prevent administration of tranexamic acid to patients similar to those in the CRASH-2 trial. The intervention is cheap, easily administered, and one of very few to be shown to reduce mortality in trauma patients.

How should we change our practice?

Administer tranexamic acid 1g intravenously in 100 mL normal saline over 10 minutes then 1 g over eight hours, starting as early as possible and no later than three hours after injury, to trauma patients who have or are at risk of major haemorrhage. Prehospital services with capacity for drug administration should consider incorporating its administration into protocols for trauma care. Do all other usual assessment and management.

Given some concerns about the generalisability of the CRASH-2 results to highly developed trauma systems, and possible unexplained harm when tranexamic acid is given more than three hours after injury, results in different contexts should be monitored. This should include appropriate screening for vascular occlusive events and vigilance for unanticipated adverse effects. Where there is capacity and sufficient clinical equipoise, confirmatory clinical trials are warranted.

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A PATIENT'S JOURNEY

Neuromuscular degeneration

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (lapsley@bmj.com) for guidance

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Previous articles in this series

- ▶ Thoracic outlet syndrome (*BMJ* 2012;345:e7373)
- ▶ Visual agnosia (*BMJ* 2012;345:e7342)
- ▶ Psychotic depression (*BMJ* 2012;345:e6994)
- ▶ Fatigue in primary biliary cirrhosis (*BMJ* 2012;345:e7004)
- ▶ Tuberculosis (*BMJ* 2012;345:e6713)

After an angina attack, Mustafa Gunaydin was prescribed cholesterol lowering drugs, which seemed to trigger neuromuscular degeneration, culminating in his death. His story is told by his partner

My partner, Mustafa, a long term smoker, underwent a single vessel angioplasty after an angina attack in September 2005, aged 55. He immediately stopped smoking and, on his doctor's advice, joined a three month rehabilitation exercise class and began taking statins (40 mg simvastatin to start with, replaced by 40 mg atorvastatin within two months). He continued to eat a healthy Mediterranean diet and take regular exercise (he was a semi-professional dancer in his youth and, having sold his business earlier in 2005 and taken early retirement, now enjoyed long walks exploring London with a friend). Although he had been a moderate drinker, in response to his health scare he cut down on alcohol. He was now free of angina, active, and positive, and said that he had never felt better.

Early signs

The first indications that all was not well came in spring 2006, when Mustafa started complaining of muscle cramps, especially at night, in his calves and thighs, usually after a long walk. By early 2007, he found it an effort to keep his arms aloft to wash his hair in the shower or to walk up even mild slopes. Sitting became uncomfortable, his neck and shoulders ached, and he experienced pain after mild exercise or even just standing for fairly short periods. He started to age visibly: his limbs lost muscle tone, his hair fell out, and he began to look permanently anxious as his confidence eroded. He had been proud of his looks and always dressed well, but now his clothes no longer fitted him and he had little spare energy to expend on his appearance.

He made several visits to his general practitioner over this period, and in August 2007 the statin dose was halved at his request. By October, his serum cholesterol level had risen to 5.4 mmol/L, but, despite the lower statin dose, his creatine kinase level continued to rise and was now at 312 units/L.

Things fall apart

He became depressed about his permanent tiredness and weakness, and obsessed with finding out what was wrong with him, spending most days reading medical reference books. This fixation developed into a loss of trust with all but a few members of the medical profession with whom he came into contact during his illness. He felt that nobody was listening to him and that any discussion he

wished to have about the documented side effects of statins and how they might be affecting him was met with a wall of silence. Two memorable remarks that contributed to his frustration were, "If you don't take the statins, you will die" (his GP) and "Ah, you're on statins, you will live forever" (a hepatologist).

A welcome turnaround

In April 2008 Mustafa decided to stop taking statins without telling his doctor. By late May, his symptoms had improved dramatically. He was able to walk long distances and up steep hills again, even in hot weather on a holiday in Turkey. The fact that his *joie de vivre* was returning was a huge boost for me too—it seemed that we could get our life back together again now that he was starting to have the energy to do the things he used to enjoy.

Reversal of fortune

At a check-up some time around the end of June, when his cholesterol level was found to have risen, he admitted that he had stopped taking statins. His GP strongly advised him to go back on them, and within a short time he was complaining of breathlessness, weakness, and backache. His GP switched him to ezetimibe (10 mg), and within 10 days he was complaining of back and leg pain and a hoarse voice. His health continued to deteriorate, and by early November his voice was weak, he was fatigued all the time, and on one memorable night had to get up seven times to urinate. He developed a suffocating sensation when lying down, and his urine became brown and cloudy, but he was told that a urine test showed nothing abnormal. However, in late November his GP told him to stop taking ezetimibe immediately: we later discovered that his creatine kinase level had reached 783 units/L at that point.

Despite stopping all cholesterol lowering drugs, he continued to decline. By early 2009, his appetite had reduced, he had worsening muscle wasting, weakness, and twitching, especially at night, and in February was admitted to hospital. His emotional state at this time was poor; he was convinced he was going to die. While in hospital, he was seen by a neurologist whose notes state that there was "muscle twitching in thighs, which are rather coarse for true fasciculations" and who diagnosed statin induced myopathy. After a week, he was discharged from hospital without any real knowledge of what was likely to happen to him.

Final months

As the year progressed, he developed an itchy rash on the back of his legs, a dry mouth, mouth ulcers, and was often cold (particularly his legs, feet, and right shoulder), especially at night. He had vivid dreams, which he would act out; he was too weak to cough and could sleep only on one side, otherwise he couldn't breathe. During June, he had increased difficulty breathing and insisted on sitting in a chair all night, as he felt he would stop breathing if he went

A DOCTOR'S PERSPECTIVE

I took over Mustafa's care in January 2009, when his health was in marked decline, and was impressed by his absolute conviction that statins had contributed to this deterioration. Understanding that cholesterol plays a vital role in cell health, particularly nerve cell function, and given the research that he presented, I took his concerns seriously. Supportive listening was probably the most important element of my care.

His inexorable decline without a clear cause was distressing and frustrating. As his GP, one of my roles was to hold an overview during his often difficult journey through the health system. He was referred to consultants from diverse specialties, each holding an important piece of the jigsaw—hepatologists (for his abnormal liver function test results), rheumatologists (for his myalgia), ENT consultants (for his hoarse voice), cardiologists (for his breathlessness), lipid clinics (for advice on statins), and neurologists (for his fatigue).

Mustafa's dying wish was that any connection between his final illness and statins be elucidated. GPs' actions are often driven by guidelines, treatment pathways, and quality and outcomes frameworks. Opportunity for careful consideration and contemplation of a disease process and manifestation is a rare luxury. Out of respect for Mustafa and concern for my profession's commitment to "do no harm," I have since spent much time researching the complex links between cholesterol, statins, and neurodegenerative disease.

Amyotrophic lateral sclerosis (ALS) is notoriously difficult to diagnose clinically, but certain aspects of Mustafa's presentation seemed inconsistent. Interestingly, symptoms were preceded by a disruption in liver function, which returned to normal on stopping statins. Mustafa presented

with proximal myopathy developing one year after starting statins. Myalgia and fatigue remained the constant feature of his illness. His symptoms improved dramatically on stopping statins and became fulminant on restarting. His muscle strength was consistently assessed as normal, even as his death approached, although his proximal musculature and voice clearly showed fatigue.

Statins are among the most commonly used drugs, and motor neurone disease very rare, complicating confirmation of a causal link. There is, however, a growing body of evidence suggesting a connection. Raised serum cholesterol is protective in ALS and a marker for prognosis. Specialist centres now stop statins in new cases of ALS. There is evidence of an association between statins and the development of "ALS-like syndrome." What is not clear is whether statins unmask ALS or induce a similar degenerative process. One postulated mechanism of statin induced neuromuscular damage is blocking of coenzyme Q10 production, a key component of the mitochondrial respiratory chain and a powerful antioxidant. Reduced coenzyme Q10 levels are noted in several neurodegenerative disorders, including ALS. Although the precise mechanism is elusive, oxidative stress and mitochondrial dysfunction are now thought to be key influences in the development of ALS.

The inquiry precipitated by Mustafa's gentle insistence has supported my growing concern that vilification of cholesterol by the statin industry is distracting attention from the underlying cause for the epidemic of degenerative disease, including ALS, namely inflammatory and oxidative stress resulting from our Western, grain based diet depleted of healthy fats and antioxidants.

Nicole Freris

to sleep lying down. His posture was poor, and his neck became very weak. Eventually his head twisted round to the left, and his right shoulder was permanently raised. Several tests confirmed progressive weakness of his proximal muscles but normal strength in his limbs.

He had an appointment with a neurologist, who agreed with the statin related diagnosis and recommended a muscle biopsy if there was no improvement in his condition over the next three months. As his condition swiftly worsened, we got an emergency appointment at the same hospital, where he saw a different neurologist, who diagnosed, with little preamble and with nine people in the room, motor neurone disease. This came as a shock to us both and a huge blow to his already fragile mental state.

Despite this diagnosis, he had no muscle stiffness, no difficulty swallowing, and he never once fell. His fine dexterity was good: he was able to dress and feed himself until a few days before he died, only eventually needing help with these tasks because he was too weak to manage on his own. Two weeks before he died he threaded a needle, changed a fuse in a plug using a screwdriver, and fastened a small fiddly necklace clasp for me. I encouraged him to do as many of these tasks as possible in an effort to contradict a diagnosis that he found too awful to contemplate.

He died in hospital on 22 August 2009 of type 2 respiratory failure (oxygen level 50% on admission to the emergency department) and two heart attacks over the course of three days.

Listening to the patient

During the last six months of his life, Mustafa came under the care of a different GP at the same practice. Dr Freris was kind and sympathetic and made appointments for him at times when I could be present too. She listened to his fears and concurred with his view that, whatever the final diagnosis, statins had had a serious effect on his health. Although it was clear to us all that he was beyond help, Mustafa always came away from those appointments feeling that he had found a doctor who understood what he was going through.

Many of the symptoms displayed during the course of Mustafa's illness—symptoms that eventually led to a diagnosis of motor neurone disease—are well documented side effects of statins and are listed in the leaflet that accompanies the tablets. With such similarities in mind, it seems wise to monitor statin-intolerant patients closely and to weigh up carefully whether the disadvantages of taking these drugs outweigh the benefits for these patients.

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