The French surgical services after the Paris and Nice terrorist attacks: what have we learnt?

Following the terrorist attacks in Paris and Nice, emergency medical services in France revised their policy on receiving mass casualties and the services' triage scenarios, summarised in *The Lancet* by Pierre Carli and colleagues (published online July 25).[1] Training takes place, including transfers of expertise from military services that improve the quality of the training.

Nevertheless, there are few emergency surgery teams available for mobilisation when there is a massive influx of traumatised patients. Academic courses focused on trauma management exist, as well as standardised training courses such as the Advanced Trauma Life Support course, the Definitive Surgical Trauma course, and the Advanced Surgical Skills for Exposure in Trauma course, etc. However, junior doctors follow the academic courses according to their motivation, and the other courses are not sufficiently promoted during the fellowship.

Like the emergency physicians, the general surgical community must train all surgeons and future surgeons to treat these types of traumatised patients in a context of mass influx of casualties. Therefore, theoretical, practical, and anatomical training must be put in place, and the authorities should assist in the implementation of these training courses.

I declare no competing interests.

Damien Massalou
massalou.d@chu-nice.fr

Université de Nice Sophia-Antipolis, Nice, 06000 France

1 Carli P, Pons F, Levraut J, et al. The French emergency medical services after the Paris and Nice terrorist attacks: what have we learnt? *Lancet* 2017; published online July 25. http://dx.doi.org/10.1016/S0140-6736(17)31590-8.

Tranexamic acid for post-partum haemorrhage in the WOMAN trial

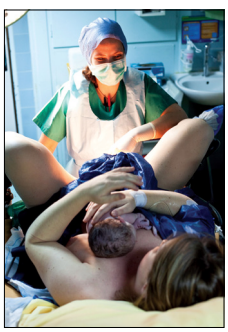
We read with interest the WOMAN trial (May 27, p 2105).[1] Tranexamic acid is an antifibrinolytic drug used to reduce haemorrhage complications in trauma and elective surgery. The WOMAN trial originally planned to enrol 15 000 women with a composite primary endpoint of death from all causes or hysterectomy within 42 days of giving birth. The trial increased the number of participants to more than 20 000 "in the hope that the trial would have enough power to detect a reduction in post-partum haemorrhage death".[1] This study reported that tranexamic acid significantly reduced the risk of death from bleeding from 191 deaths (1·9%) to 155 deaths (1·5%; p=0·045).[1] Further reductions in death occurred when tranexamic acid was given within 3 h of giving birth (1·7% *vs* 1·2%; p=0·008). Reduction in mortality from all causes was not significantly different between the tranexamic acid group and the placebo group (p=0·16). The WOMAN Trial Collaborators concluded that "when used as a treatment for post-partum haemorrhage, tranexamic acid should be given as soon as possible after bleeding onset".[1]

We strongly believe that such a conclusion is premature and might be misleading to health-care professionals and the public. Moreover, the following statement is cited on the chief investigator's institutional website and also appears in videos and on social media platforms: "tranexamic acid could save the lives of one in three mothers who would otherwise bleed to death after childbirth". We believe that such statements seem to misrepresent the data.

How is tranexamic acid known to reduce death from post-partum haemorrhage and how is p=0·008 (or p=0·045) interpreted when the cutoff value to reject the null hypothesis is p=0·05? Statistically, it means that eight in 1000 chances exist for being wrong, which sounds compelling, but there are limits. In the WOMAN trial, p=0·008 denotes a 0·8% probability of observing a mortality difference of 0·5% (1·7–1·2%) under the null hypothesis, and would indicate that the null hypothesis should be rejected. However, establishment of the magnitude of difference between the tranexamic acid and placebo groups requires the CI. The CI was 0·52–0·91, which is wide and lessens the strength of the data to support the use of tranexamic acid. Analysis of the population of patients who died from bleeding also showed statistical significance between tranexamic acid and placebo groups (p=0·045); however, on closer inspection the CI of relative risk includes the null value of 1 (0·65–1·00). Therefore, the significant differences in the WOMAN trial appear to be marginal at best.

Another important question is whether a 0·4% or 0·5% difference in mortality reduction is clinically relevant. The problem is that any small difference will be statistically significant if the sample size is large enough, regardless of clinical relevance. As stated by Houle and Stump,[2] "many large clinical trials obtain a high level of statistical significance with miniscule differences between groups, which are completely clinically irrelevant. However, with proper marketing, billions can be made from results of dubious clinical importance". Judgments about clinical importance should be formed on the basis of the size of the effect and CIs instead of the p value, because the p value is strongly affected by the size of the study.[3,4] If the study kept its original sample size of 15 000, would the results be different?

Finally, the WOMAN trial does not adequately address clinical issues about optimum timing and dose. What laboratory tests are recommended to drive the clinical use of tranexamic acid? Similar questions emerged from



Science Photo

For more on the **institutional website** see http://womantrial.lshtm.ac.uk/

the CRASH-2 trial,[5] which continues to generate controversy. Although we agree that global action for maternal health should be accelerated and not diminished, the results of the WOMAN trial are only the beginning stages towards this goal. Tranexamic acid should not constitute a one-size-fits-all approach to treat blood loss but provide a basis for more precision-based discussions to reduce maternal mortality and morbidity supported by basic science.

We declare no competing interests.

*Hayley L Letson, *Geoffrey P Dobson*
geoffrey.dobson@jcu.edu.au

Heart, Trauma and Sepsis Research Laboratory, College of Medicine and Dentistry, James Cook University, Townsville City, QLD 4811, Australia

1 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389:** 2105–16.
2 Houle TT, Stump DA. Statistical significance versus clinical significance. *Semin Cardiothorac Vasc Anesth* 2008; **12:** 5–6.
3 Cleophas TJ. Clinical trials: renewed attention to the interpretation of the p values—review. *Amer J Therap* 2004; **11:** 317–22.
4 Biau DJ, Jolles BM, Porcher R. P value and the theory of hypothesis testing: an explanation for new researchers. *Clin Orthop Relat Res* 2010; **468:** 885–92.
5 Walsh M, Shreve J, Thomas S, et al. Fibrinolysis in trauma: "myth," "reality," or "something in between". *Semin Thromb Hemost* 2017; **43:** 200–12.

We read with interest the WOMAN trial[1] and commend the investigators on this important multicentre, international, placebo-controlled trial. For a study to have external validity, its conditions need to be representative of a larger population. This study was mainly done in low-income and middle-income countries; thus, we have concerns about its generalisability. Many differences probably exist in the health-care systems (and disease burdens) between many countries included in the trial. Therefore, we do not think the results are immediately translatable to high-income countries.

In the trial, the incidence of death from post-partum haemorrhage (but not overall mortality) was 1·9% and reduced to 1·4% with tranexamic acid. Based on the data, the number needed to treat was 250 women. In Australia, 11 deaths from haemorrhage occurred over a 5-year period.[2] If the post-partum haemorrhage incidence was 5% and the same relative risk and risk reduction as the WOMAN trial was used, the number needed to treat in this setting is approximately 35 587 women.[3]

The mechanism of death in obstetric haemorrhage is likely to differ in low-income and middle-income countries. Death from hypovolaemic shock rather than death from complications of haemorrhage, such as transfusion-related acute lung injury, multiorgan failure, acute respiratory distress syndrome, and sepsis is unlikely to occur in high-income countries. In low-income and middle-income countries, with no interventional radiology, cell saver, ready access to blood transfusion, staffed operating theatre, or intensive care unit, simple hypovolaemia is more likely to be the mechanism. In the era of evidence-based medicine and as health-care professionals caring for pregnant women, we need to ask does this specific paper provide the evidence that we should use to change our practice. Although the absence of major adverse effects (most particularly thrombotic complications) is reassuring, on the basis of the number needed to treat and the different contexts in which this study was done, tranexamic acid should not be routinely included in the management of obstetric haemorrhage in women from high-income countries.

We declare no competing interests.

**Alicia Therese Dennis, James D Griffiths*
adennis@unimelb.edu.au

Department of Anaesthesia, The Royal Women's Hospital, Parkville, VIC 3052, Australia (ATD, JDG); and Department of Obstetrics and Gynaecology (ATD) and Department of Pharmacology (ATD, JDG), University of Melbourne, Melbourne, VIC, Australia

1 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389:** 2105–16.
2 Humphrey MD, Bonello MR, Chughtai A, Macaldowie A, Harris K, Chambers GM, for Australian Institute of Health and Welfare. Maternal deaths in Australia 2008–2012. 2015. http://www.aihw.gov.au/publication-detail/?id=60129551119 (accessed May 16, 2017).
3 Australian Institute of Health and Welfare. National Maternity Data Development Project: primary postpartum haemorrhage—research brief no. 8. 2016. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=-60129554616 (accessed May 16, 2017).

As one of the many collaborators who contributed to the WOMAN trial[1] our team's involvement in research that will improve maternal outcomes globally has been gratifying. 1 g of intravenous tranexamic acid given within 3 h of post-partum haemorrhage significantly reduced maternal death and the need for surgery (laparotomy). The fact that post-partum haemorrhage was defined as 500 mL or more for vaginal deliveries but 1000 mL or more for caesarean section is important to note. This difference should be considered when clinicians update local guidelines for post-partum haemorrhage.

Recruitment from high-income countries was halted after a prespecified number of participants had consented, with the trial continuing in low-income and middle-income countries. The WOMAN trial was pragmatic, with the intervention given in addition to standard drug treatment or interventions. It would be useful to know whether subgroup analysis was possible in participants recruited in high-income countries with healthier populations, where standard drug intervention was available and given, and how this affects the numbers needed to treat to achieve either of the two significant outcome benefits.

Finally, extrapolation of the trial results should be avoided. Intervention was limited to those with post-partum haemorrhage (500 mL for vaginal

delivery; 1000 mL for caesarean section; or estimated blood loss enough to compromise the woman's haemodynamic status) and tranexamic acid was not used prophylactically. In early discussions with colleagues, some are already considering whether intravenous tranexamic acid should be used as routine prophylaxis for all caesarean sections and even all vaginal deliveries. However, such intervention is not justified by the results from this trial.

I contributed to the recruitment in the WOMAN trial and was listed as one of the WOMAN Trial Collaborators.

Kim Hinshaw
kim.hinshaw@chsft.nhs.uk

Department of Obstetrics, Sunderland Royal Hospital, Sunderland, Tyne and Wear SR4 7TP, UK

1 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389:** 2105–16.

As clinicians and researchers of post-partum haemorrhage, we appreciate the clinical trial of tranexamic acid[1] and applaud the researchers and results. We want to emphasise the importance of the addition of tranexamic acid to other technologies and strategies to form a complete comprehensive package for post-partum haemorrhage (or emergency post-partum haemorrhage bundle),[2] which begins at the community level and proceeds, with attention to context, through primary health care to the referral-hospital level. As the authors note, tranexamic acid was tested at higher-level facilities (ie, secondary and tertiary hospitals) with providers not only able to give intravenous injections, but who were skilled enough (and equipped) to deliver a 1 mL/min dose of 1 g tranexamic acid, do hysterectomy or laparotomy, and give blood transfusions. Furthermore, the findings suggested early (<3 h) treatment with tranexamic acid, which is not always possible given the distances and delays women face in the settings of the community or primary health care. It could be some time before the bioavailability and correct dose of alternative routes have been trialled. For now in the setting of the community or primary health care, in which intravenous injections are neither safe nor feasible, and in higher-level facilities, in which a woman could arrive more than 3 h after the haemorrhage starts, a comprehensive continuum of care for post-partum haemorrhage is needed.[3] At lower-level health-care facilities (ie, primary health care and dispensaries) the uterine balloon tamponade (as a packaged kit)[4] and non-pneumatic antishock garment[5] could save lives and buy time for referral and transportation delays. These interventions should be used together when necessary (in cases of shock) and should both decrease blood loss and cause clot formation, so that they can be effective with tranexamic acid.

SM holds a faculty position at the University of California, San Francisco, which holds the right to the trademark LifeWrap (one brand of NASG) and has licensed this trademark to the BlueFuzion Group. BlueFuzion Group pays the University of California, San Francisco a royalty of 2·5% for the use of the trademark LifeWrap. All other authors declare no competing interests.

**Suellen Miller, Thomas Burke, José M Belizán, Carlos Fuchtner, Andre Lalonde, Jaideep Malhorta*
suellen.miller@ucsf.edu

Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine, University of California, San Francisco, San Francisco, CA 94158, USA (SM); Department of Emergency Medicine, Division of Global Health and Human Rights, Massachusetts General Hospital, Boston, MA, USA (TB); Department of Mother and Child Health Research, Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina (JMB); International Federation of Gynecology and Obstetrics, Barrio Equipetrol Norte, Santa Cruz de la Sierra, Bolivia (CF); Department of Obstetrics and Gynecology, University of Ottawa, Ottawa, ON, Canada (AL); Department of Obstetrics and Gynecology, McGill University, Montreal, QC, Canada (AL); and Rainbow Hospitals, Agra, Uttar Pradesh, India (JM)

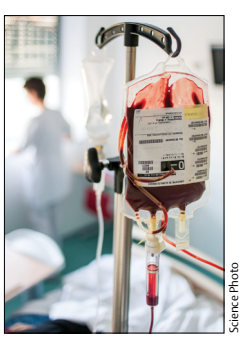
1 WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389:** 2105–16.

2 Council on Patient Safety in Women's Health Care. Patient safety bundle—obstetric hemorrhage. 2015. http://safehealthcareforeverywoman.org/patient-safety-bundles/obstetric-hemorrhage/ (accessed July 19, 2017).

3 Kapungu CT, Koch A, Miller S, Geller SE. A community-based continuum of care model for the prevention and treatment of postpartum hemorrhage in low resource settings. In: Arulkumaran S, Karoshi M, Keith LG, Lalonde AB, B-Lynch C, eds. A comprehensive textbook of postpartum hemorrhage, 2nd edn. London: Sapiens Publishing Limited, 2012: 555–61.

4 Burke TF, Ahn R, Nelson BD, et al. A postpartum haemorrhage package with condom uterine balloon tamponade: a prospective multi-centre case series in Kenya, Sierra Leone, Senegal, and Nepal. *BJOG* 2016; **123:** 1532–40.

5 Pileggi-Castro C, Nogueira-Pileggi V, Tuncalp O, Oladapo OT, Vogel JP, Souza JP. Non-pneumatic anti-shock garment for improving maternal survival following severe postpartum haemorrhage: a systematic review. *Reprod Health* 2015; **12:** 28.



Science Photo

In their international randomised controlled trial, the WOMAN Trial Collaborative Group[1] showed that early administration of tranexamic acid significantly reduced death due to bleeding in patients with post-partum haemorrhage. However, they did not mention how transfusion therapy was administered in the study cohort.

It should be noted that prompt replacement of blood components is important if massive haemorrhage has occurred or is likely to occur.[2] To start blood transfusion as soon as possible, a transfusion sector should store a sufficient amount of type O-negative and O-positive blood, which has not been crossmatched.[3] The ratio of blood component is also important. To prevent dilute coagulopathy, some guidelines recommend that a 1:1 ratio of red blood cell to fresh frozen plasma should be administered until laboratory measurements that adjust the therapy are available.[2,4]

However, not all transfusion sectors would be able to prepare such a system, and the supply system of blood transfusion would differ substantially between facilities. Since the WOMAN trial was an international study, in which patients were enrolled from 193 hospitals in 21 countries,