Injury, Int. J. Care Injured 45S (2014) S20–S28

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

# Female sex protects from organ failure and sepsis after major trauma haemorrhage☆

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ARTICLE INFO

*Keywords:*
Multiple trauma
Blunt trauma
Trauma registry
Sex
Sex hormones
Haemorrhagic shock
Mortality
Risk factors
Age factors

ABSTRACT

*Introduction:* Biological sex is considered a risk factor for adverse outcome after major trauma. We hypothesized that female sex is protective against organ failure, sepsis and mortality in patients with traumatic haemorrhage.

*Patients and methods:* We selected patients from TraumaRegister DGU® (TR-DGU) with primary admission for blunt trauma with an injury severity score ≥16 and an ICU stay ≥3 days that presented with relevant bleeding in the years 2007–2012. Relevant bleeding was defined as Abbreviated Injury Scale (AIS) ≥3 with an estimated blood loss exceeding 20%, any femoral shaft fracture, any pelvic clamp as surrogate for unstable pelvic fracture or the presence of at least one criteria of haemorrhagic shock: shock index of 0.8–1.4; base excess of −2.0 to −10.0 mmol/L; body temperature ≤34 °C; transfusion of ≥4 units of packed red blood cells; application of recombinant activated factor VII; any embolization during trauma room phase and pre-hospital resuscitation volume ≥3000 ml or any catecholamine use during pre-hospital care in the absence of cardiopulmonary resuscitation. A total of 7560 males and 2774 females were selected and analyzed for sex differences.

*Results:* Higher rates of multiple organ failure (24.4 vs. 21.3%, Odds ratio [OR] 1.19 (95% confidence interval [95%CI] 1.07–1.33), $p = 0.001^*$) and sepsis (16.5 vs. 11.3%, OR 1.55 (95%CI 1.35–1.77), $p < 0.001^*$) were observed in males. Organ function of lung, cardio-circulatory system, liver and kidney were better in females, however, there was no difference in mortality. Stratification by age group revealed that in particular age-group 16–44 years was related to improved organ function which may indicate effects of sex hormones in females at reproductive age. Increased rates of sepsis in males were observed throughout virtually all age groups starting at 16 years of age, except in age group 54–64 years. This may suggest suppressive effect of testosterone on immune function.

*Conclusions:* Our study supports the hypothesis that female sex is associated with improved organ function following traumatic injury and haemorrhagic shock, in particular in age groups that are at reproductive age. However, further studies are warranted before sex steroids can be deployed as therapeutic intervention in critically ill trauma patients.



## Introduction

A broad variety of various factors including outcome endpoints such as survival and the onset of multiple organ failure (MOF) or septic complication determines the response to severe injury. Based on experimental data, biological sex is one factor that is well recognized as a modulator of the inflammatory response [1–4] and cardiovascular function [5–7]. Improved cardiac function and vascular dilation has been related to menstrual circle in females. This observation has been correlated with activity of the

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http://dx.doi.org/10.1016/j.injury.2014.08.013
0020–1383/

endothelial regulation of nitric oxide synthases (eNOS) and expression of oestrogen receptor alpha (ER-α) [5,6,8].

Although clinical findings are controversial, there are some clinical studies that have described improved outcome in females [9,10]. George et al. reported higher rates of renal failure in males after blunt trauma but no difference in pulmonary failure [11]. Recently, we have described lower rates of MOF following trauma particularly in females aged 16–44 years [12]. Similar findings were described by Mostafa et al. who concluded that lower rates organ failure (OF) in females aged 15–45 years was possibly the result of sex-steroid effects [13].

Shock is known as an independent risk factor for MOF following major trauma [14]. Clinical [14–16] and experimental [5,17–21] data indicates that females seem to be protected against such consequences of shock. They also seem to have a better physiologic response to similar degrees of shock and trauma. In a prospective clinical study, Deitch et al. report data including more than 4000 trauma patients. They have found that premenopausal women have lower initial serum lactate levels and received less blood transfusion, while having a greater magnitude of injury [16]. Another prospective clinical study identifies females to required lower resuscitation volume and less Starling curve intervention in order to maintain a designated goal for oxygen delivery. The authors conclude that females respond better to standardized resuscitation compared to similarly injured males [14].

In experimental models of trauma haemorrhage, Deitch et al. show that the haemodynamic response in proestrus female rats (i.e. phase of the cycle with high oestrogen levels) was better preserved during shock than in males. This was manifest as better maintenance of cardiac output and systemic vascular resistance. Likewise, better microcirculatory blood flow was observed in heart, lung, kidney, intestine as well as non-intestinal splanchnic organs such as liver, spleen, and pancreas. Moreover, only in female rats there was a consistent increase in organ blood flow following volume resuscitation. In contrast, in male rats following trauma-haemorrhage, the level of organ blood flow, especially to the splanchnic organs, remained similar to that observed during the shock period [18].

The underlying mechanisms of female sex hormones on the response to shock are not yet fully understood although it is obvious that 17-β-oestradiol or oestrogen-receptor agonists preserve trauma-haemorrhage induced organ damage. A recent study by Doucet et al. indicates that oestrogen suppresses enteral inducible nitric oxide synthases (iNOS) that is involved in the pathogenesis of ischaemia-reperfusion-mediated intestinal injury in a number of models and whose activity is mediated via oestrogen receptor beta (ER-ß) and to lesser extent ER-α. Moreover, the investigators observed reduced rates of bacterial translocation, villous injury of ileum epithelium, increased lung permeability and an increased degree of lung neutrophil sequestration in rats following trauma-haemorrhage. Excessive production of iNOS-derived nitric oxide as well as the generation of reactive oxidants is considered the key to shock-related gut injury that via bacterial translocation and release of biological active lymph leads to induction of an inflammatory response at remote organ tissue and thus leads to organ failure [19].

Childs et al. also demonstrate that 17-β-oestradiol inhibits haemorrhagic shock-induced vascular leakage in a rat model of trauma-haemorrhage, mediated through oestrogen receptors. Moreover, they found that 17-ß-oestradiol has a protective role on the endothelial cell barrier that regulates vascular leak at least partially mediated through the inhibition of the mitochondrial-mediated "intrinsic" apoptotic signalling pathway [17]. Hsu et al. found that 17-β-oestradiol prevents trauma-haemorrhage induced impairment in cardiac function via Akt-dependent heme oxygenase-1 up-regulation [22]. Moreover, oestrogen can attenuate the trauma-haemorrhage-induced increase in lung extracellular-signal regulated kinase (ERK) phosphorylation, which is associated with increased lung myeloperoxidase activity, wet-to-dry weight ratio, interleukin (IL)-6, tumour necrosis factor (TNF)-alpha, intercellular adhesion molecule (ICAM)-1, cytokine-induced neutrophil chemoattractant (CINC)-1, and macrophage inflammatory protein-2 levels. These data suggest that the salutary effects of 17-β-oestradiol on lung after trauma-haemorrhage are mediated via an ERK pathway and subsequent down-regulation of pro-inflammatory mediator production [23].

Based on these observations, we hypothesized that females withstand trauma-haemorrhage better than males following severe trauma. Thus, we would expect lower rates of organ failure and sepsis in females suffering major blood loss from traumatic injury and that this effect would be expected to be most noticeable in females of reproductive age because in such individuals high levels of female sex hormones would be most evident. The aim of the present study is to test this hypothesis based on data from the TraumaRegister DGU® (TR-DGU).

## Patients and methods

### *TraumaRegister DGU® (TR-DGU)*

Patient data was obtained from TraumaRegister DGU® (TR-DGU) of the German Trauma Society (Deutsche Gesellschaft für Unfallchirurgie, DGU). This registry is a large, multi-centre database that serves as an obligatory tool of quality assurance for trauma centres participating in the TraumaNetzwerk DGU®. Data is gathered using a standardized form containing more than 100 variables on clinical data as well as laboratory chemical markers from time points during pre-hospital treatment (time point A), at emergency room (ER) admission (time point B) and throughout the hospital course including intensive care unit (ICU) admission and ICU course (time point C), Moreover it contains details on full pattern of injury, all surgical therapies and status by the time of hospital discharge (time point D) as described on the TR-DGU homepage (www.traumaregister.de), where a comprehensive list of participating trauma centres is also provided. By the time of the analysis the registry holds more than 122,000 datasets of severely injured trauma patients.

### *Patients and definitions*

With reference to a previous study on sex-related differences in outcomes using TR-DGU data from 1993 to 2006 [12], we limited the number of eligible patients to the years from 2007 to 2012 in order to ensure the independence of results. Furthermore, eligible patients were required to have their data collected according to TraumaRegister DGU® standard data entry form ($n = 55{,}352$ datasets). Patients whose data were recorded according to the reduced QM data entry form do not provide all items required for a full scientific analysis and thus were excluded. Inclusion criteria were primary trauma admission for blunt trauma with ISS $\geq$16 points and three or more days of ICU stay who presented with relevant bleeding.

Relevant bleeding was defined according to Abbreviated Injury Scale (AIS) $\geq$3 with an estimated blood loss exceeding 20% of the total body blood volume according to Abbreviated Injury Scale® Version 2005 Update 2008. Thus, we selected all patients with the appropriate AIS codes excluding all codes for penetrating injuries. Moreover it was considered for all patients who were operated on for femoral shaft fractures as identified by OPS procedural codes 5-786.6 (intramedullary nail), 5-786.8 (external fixator), 5–786.2 (ORIF with plate) or 5-786.k (locking-screw plate) at any point during hospital stay and for all patients provided with a pelvic