Left of Bang Interventions in Trauma: Ethical Implications for Military Medical Prophylaxis

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ABSTRACT

Advances in medical capability should be accompanied by discussion of their ethical implications. In the military medical context there is a growing interest in developing prophylactic interventions that will mitigate the effects of trauma and improve survival. The ethics of this novel capability are currently unexplored. This paper describes the concept of trauma prophylaxis (Left Of Bang Interventions in Trauma) and outlines some of the ethical issues that need to be considered, including within concept development, research, and implementation. Trauma prophylaxis can be divided into interventions that do not (type 1) and those that do (type 2) have medical enhancement as an unintended side effect of their prophylactic action. We conclude that type 1 interventions have much in common with established military medical prophylaxis, and the potentially enhancing qualities of type 2 interventions raise different issues. We welcome further debate on both interventions.

INTRODUCTION

Combat trauma can have devastating effects on both survival and long-term physical and psychological function. Modern trauma care for the war-wounded has advanced markedly during the recent conflicts in Iraq and Afghanistan. Further improvements may require a conceptual shift towards medical intervention *before* injury occurs. Eisenstein *et al* outlined such a strategy, coining the term “Left Of Bang Interventions in Trauma” (LOB-IT), as a reference to traditional military medical timeline schemata where events are depicted as occurring from left to right as time progresses. A LOB-IT is *“any medical, pharmacological, or surgical intervention that is delivered before trauma in order to reduce morbidity and mortality following injury”*[1]. Recently, there has been an increase in basic science and observational clinical studies exploring the potential for LOB-IT to

improve mortality and outcomes after injury.[2-5] No LOB-IT has yet been tested in humans, but may be justified if further improvements in trauma survival and outcomes are to be realised. Trials of LOB-ITs may raise ethical concerns given the novelty of the ideas involved and the military context. In this paper we will summarise and explore some of these concerns in relation to the ethics of prophylaxis use, clinical research, military medicine, and human enhancement, in order to promote further discussion amongst civilian and military ethicists alike.

There are two ethically distinct categories of LOB-ITs: Type 1 are those that are purely prophylactic; and Type 2 are those that may have both prophylactic and enhancing properties (for example a beneficial augmentation of strength or physical reserve in addition to their prophylactic effects).[6] A hypothetical example of a Type 1 LOB-IT may be tranexamic acid (TXA), and, an equally hypothetical example of a Type 2 LOB-IT may be erythropoietin (EPO) (see Table 1). For the purpose of this paper, we will assume that any performance-enhancing side-effects of LOB-ITs are unintended consequences of a primary intention to reduce morbidity and mortality after trauma. Nonetheless, the ethical implications of these enhancement properties cannot be ignored.

Table 1. Examples of potential Type 1 and Type 2 left of bang interventions in trauma

Type of intervention	Rationale
Type 1 Eg. Tranexamic acid (TXA)	Reduces mortality after trauma. The earlier TXA was given after injury, the greater its effect on reducing mortality.[7] Routine administration of TXA preoperatively reduces blood loss.[8]
Type 2 Eg. Erythropoietin (EPO)	May confer survival advantage if given before trauma due to its enhancing effects on red blood cell number and volume (well known through its use as a performance-enhancing drug in competitive sports.[4, 9])

TYPE 1: PURELY PROPHYLACTIC LEFT-OF-BANG INTERVENTIONS

Current military use of prophylaxis centres on infectious diseases. Vaccinations and anti-malarial drugs are routinely offered to military personnel when the level of risk from the infectious disease and the benefits of avoiding or ameliorating infection outweigh the risks from the prophylaxis. Both trauma and infectious diseases are threats to life and health that can be predicted temporally and geographically. In addition, both cause a significant burden to military personnel and capability, and the deleterious effects of both may be mitigated through the use of prophylaxis. However, whilst there is significant evidence of the efficacy of infectious disease prophylaxis, there are no human data for trauma. The acceptability of trials to test the potential benefits of such an intervention may depend upon an understanding and acceptance of the ethical equivalence between Type 1 (non-enhancing) LOB-IT and current prophylaxis. The advent of pre-exposure prophylaxis (PrEP) for HIV infection has resulted in a renewed interest in the principles of prophylaxis more generally (Table 2).

Table 2 – Ethical Principles of Prophylaxis Relevant to LOB-IT (from Sugarman and Mayer 2013[10] and WHO 2014[11])

Wellbeing / Utility	The benefits of the prophylaxis must outweigh the harms
Safety	Apart from direct side effects, consideration must be given to the potential risks of the prophylaxis, e.g. consequences of imperfect adherence
Parameters of Use	If data on safe and effective use is limited, prophylaxis must only be used within the limits of these data, i.e. generalisability to different populations or uses must not be assumed
Risk Behaviours	Steps must be taken to educate recipients about avoidance of risk compensation and to monitor changes in risk-related behaviour
Stigma	Consideration must be given to how others may perceive those receiving prophylaxis, e.g. difficulties obtaining insurance
Diversion	In resource poor settings, there is a possibility that drugs that can be used to treat extant conditions are diverted to prevent the same or other conditions
Equity / Justice	There should be a fair distribution of risks and benefits amongst the relevant population
Access	Prophylaxis must be acceptable to the population at risk. This includes both the formulation of the treatment and the system of provision
Competing Priorities	Consideration must be given to how to distribute risks and benefits fairly. What “fairness” means may change over time and depends on available resources, risk environment, and societal norms

Utility

Like any prophylaxis, there needs to be a careful analysis of the balance of risks and benefits of either taking or not taking LOB-ITs. In the context of trauma, this analysis will have to take account of the likelihood, severity and timing of injury, the efficacy of the prophylaxis, any adverse effects, and any possible impact of prophylaxis on risk-taking behaviour. LOB-IT is a new concept and currently has no direct data to inform our understanding of the magnitude of risks and benefits of the equation. Whilst significant historical and pre-clinical data are available, the principle of ‘Parameters of Use’ (Table 2)

demands that clinical trials will be required to establish safety and efficacy. Such trials would need to conform to the accepted ethical frameworks for clinical research. These are summarised in Table 3.

Table 3: Ethical Principles of Clinical Research (Modified from Emanuel *et al.* 2000[12] and NIH Clinical Research Guidance 2016[13])

Social and clinical value	The answer to research question must be of value to society
Scientific validity	The research question must be answerable and the methods used to do so must be valid and feasible
Fair subject selection	The scientific goals of the study (rather than unrelated factors) should dictate the choice of group from which individuals are chosen
Favourable risk-benefit ratio	The risks to the participants must be minimised and must be proportional to the potential benefit to society
Independent review	An independent review panel should review the proposed research to prevent bias, protect participants, assess risks and benefits, and ensure that the research is ethical
Informed Consent	Subjects must: 1) Be informed of the risks, benefits, purpose, alternatives, and methods of the research, 2) Understand how this research relates to their own interests, 3) Make their decision about whether or not to participate voluntarily
Respect for potential and enrolled subjects	Researchers should have respect for participants' privacy and their right to change their mind about on going involvement in the research. Participants' welfare should be monitored during and after the study. Researchers should share the study findings with the participants

Accountability and responsibility

Even if Type 1 LOB-ITs are to be considered ethically equivalent to other forms of prophylaxis, they still raise ethical issues in relation to acceptability and corporate responsibility. Prophylaxis in the military has not been without controversy, with widely publicised debate surrounding biological and chemical weapon prophylaxis in the first

Gulf War, as well as more recent criticism of the choice of antimalarial prophylaxis agents. [14-16] Controversies such as these have the potential to erode trust in military medical prophylaxis despite little evidence of harm attributable to these prophylaxes. Thus, if LOB-ITs are going to be acceptable for use, it will not be sufficient to ensure safe, open, and ethical trials; it will also be necessary to consult potential user groups about the very idea of LOB-IT in advance of such trials.

One may ask whether LOB-IT is solely a military medical issue. The answer is that the population LOB-IT is most likely to benefit is that of the military because this population has a high and a potentially predictable risk profile. Even within the military, there are only particular sub-populations and activities that would confer a sufficiently high level of risk to justify the administration of LOB-IT. Thus, given that the population at risk is a military one, special ethical considerations of military medicine also apply.

Special military considerations

One of the key ethical challenges in military medicine is the balance between respect for individual autonomy and wellbeing, and the achievement of military objectives. Medical interventions have a special ethical status both in civilian and military settings. To illustrate this special status one can compare the ethics of non-medical versus medical protection. In the UK armed forces, combatants are ordered to wear personal protective equipment (PPE) such as body armour and hearing protection despite theoretical risks of heat injury or reduced situational awareness respectively. Ordering individual combatants to wear PPE is justified because the benefits (protection from ballistic wounding and noise-induced hearing loss respectively) outweigh the risks. Moreover, an injured individual may affect operational effectiveness of the entire formation. Medical prophylaxis, however, is not regarded in the same way. If combatants decline to take

prophylaxis, there may be adverse consequences of so doing such as exclusion from military operations in endemic areas, and they may face sanctions (from the non-medical chain of command) for deliberately rendering themselves unfit for duty. One difference in approach to compulsion is that medical prophylaxis is prescribed by doctors, who have to adhere to their professional code of conduct as well as to military codes (previously described as “dual-loyalty[17]). The former prohibits coercive treatment in most circumstances partly out of respect for individual patient autonomy and partly to protect individual doctor-patient relationships. Public health may be an exception to this general rule. Here the interests of the population may override those of the individual. The state can legislate to provide prophylaxis to entire populations e.g. fluoridation in water, folic acid in bread, though unlike vaccinations – which are compulsory in some jurisdictions – these measures are not prescribed or administered by doctors/healthcare professionals. Furthermore, even when individuals cannot be forced to receive treatment in their own interests, they can face compulsory quarantine in the interests of the population.

The military forms a particular community within the general population and operates to different norms. In most NATO-allied nations, the decision to join the armed forces is a *prima facie* voluntary one. Its voluntariness has, however, been questioned. The socio-economic and race structure of, particularly, the US military, a paucity of other job opportunities in generally disadvantaged groups, and opportunities such as free/subsidised education and free/subsidised medical care provided to family members of serving personnel may result in some economic coercion to join the military.[18] Enlistment is, however, undertaken in the knowledge that it entails a significant reduction in self-determination (e.g. the requirement to wear a uniform, loss of privacy, obedience to the chain of command including to being placed in harm’s way). In addition, other

values gain heightened significance. In the British Army, for example, these are institutionalised as “The Army’s Core Values”: courage, discipline, respect for others, integrity, loyalty, and selfless commitment.[19] Adherence to these values, when combined with some loss of self-determination, may impact on the way that decisions are made in terms of consent and cooperation with large scale prophylaxis programmes, including potential LOB-ITs. The emphasis on selflessness and loyalty may mean that military personnel are more likely to feel a moral obligation to agree to being exposed to LOB-ITs, even if there were no obvious gains for the individual. Furthermore, practicing courage and integrity may lead military personnel to consider adherence to prophylaxis guidelines one of their duties, even if those interventions have uncertain efficacy. These factors, the voluntariness, or otherwise, of the decision to join the military, a reduction in self-determination of soldiers and adherence to institutionalised values may vary from military to military and, indeed between individuals in the same military and should be taken into account when developing novel medical interventions.

The interplay between wider social norms and rights, and those governing military service is therefore a complex one. Drugs prescribed and ingested during ‘on-duty’ periods will continue to have effects during ‘off-duty’ periods (and may have life-long consequences), as indeed may the regimes of physical exercise. Military medical professionals are both subject to the military chain of command and are required by their professional regulatory bodies to adhere to professional codes of conduct whenever and wherever they are practicing. The tension that this creates for practitioners is well known, with some arguing that that doctors’ professional ethics pertain even when they practice in the military environment, whilst others assert that the military context calls for a fundamental re-understanding of military medical ethics.[17, 20]

Military organisations make considerable investments in their medical services; especially those that address immediate combat injuries. In addition, heroic efforts may be made to retrieve and evacuate injured personnel putting further lives at risk. However, despite these significant financial and manpower commitments, medical resources may be limited for reasons of operational necessity. An injured combatant may use resources that will not then be available for the next casualty and these implications merit consideration in the military setting, as we will now discuss. Civilian patients are not normally expected to consider the interests that other patients might have in the resources necessary to treat them. This does not, however, mean that patients do not have responsibilities to protect themselves against adverse health events and to limit demands on health services.[21] These responsibilities may be heightened when the costs and benefits of resources are shared not impersonally between fellow citizens, but between close friends or family members. Consider, for instance, live kidney donation by parents to their children where parents willingly undertake burdens and risks to their health to benefit that of their child. Combatants share a special relationship that may be closer to that of family members than that of a group of strangers. Moreover, in combat scenarios the uninjured survival of each member of the group adds to the chances of survival of the whole group. Each member of the group has a vested interest not only in being uninjured themselves, but also in their fellow members being uninjured. Measures that lessen the chances or impact of injury are, therefore, arguably in the interests of all. Respect for autonomy may justify affording individuals the freedom to take risks that affect only themselves. It is less clear that individuals should be similarly free to do as they wish when it comes to taking risks that have negative consequences for others. Consideration going forward, therefore needs to be given to whether individual

combatants at particularly high risk could be required to take prophylaxis in these circumstances. The values and norms of the military community suggest that individuals should (or are likely to) be *willing* to take prophylaxis in the interests their colleagues but this is in part an empirical question that also requires further investigation.

Are type 1 left-of-bang interventions different to other forms of prophylaxis?

Two common threats that current military prophylaxis seeks to mitigate are infectious disease and chemical agent injury. Infectious disease differs because vaccines and other prophylaxis (such as for malaria) may completely prevent the disease occurring in the first place. In contrast, chemical weapon prophylaxis and LOB-ITs can only reduce mortality and morbidity, not eliminate them altogether. Another difference is that infectious disease prophylaxis can confer herd immunity (where subtotal administration in a population confers protection to those who have not received the prophylaxis because the reservoirs and / or vectors of that disease are reduced) whereas other prophylaxis cannot do so. As discussed above, LOB-IT-unprotected individuals within a largely LOB-IT-protected group may still gain a survival advantage because the group may have an overall greater chance of survival. From a pragmatic standpoint, LOB-ITs have more in common with prophylaxis against chemical weapons than prophylaxis against infectious disease. Since chemical weapon prophylaxis is current accepted practice in the appropriate threat environment, Type 1 LOB-ITs could be similarly justified.

Might trauma prophylaxis encourage more risky behaviour?

One question relating to all prophylaxis is whether or not it leads to “risk compensation”.[22] The basis of risk compensation is that a perceived protection from risk may lead to higher-risk behaviour, and thus an equal or greater overall risk to the individual (or group). In the military context this could result in individuals being more

willing to take risks during combat, which could be seen as beneficial to the combat effort if this increases the likelihood of achieving the mission objective. Equally, a commander might be willing to accept greater risk to his/her troops if he/she thought that they were protected by prophylaxis. This phenomenon has been discussed in non-military contexts, particularly when relating to cycle helmet wearing and HIV prophylaxis, but high quality evidence of a consistent effect is lacking and the relevance to the military context is unknown.[23, 24] In any future LOB-IT discussion or trials, attention must be given to the second order effects, such as impact on the decision-making of the chain of command or individuals, as well as the purely medical effects.

TYPE 2: PROPHYLAXIS WITH POTENTIAL ENHANCEMENT

In addition to a survival or trauma mitigation advantage, some LOB-ITs might confer a performance advantage that can be defined as an enhancement (see Table 1). Juengst described an enhancement as a medical or biological intervention designed “to improve performance, appearance or capability besides what is necessary to achieve, sustain or restore health”.[25] Some interventions that are banned in competitive sports are considered to increase the physiological reserve of those taking them, resulting in improved strength and stamina. The potential military advantages of enhancement interventions may be, for example, that those taking them are able to carry heavier loads (ammunition, weapons, water, rations), travel further, and fight for longer.

The arguments against the use of performance enhancing drugs in competitive sport range from issues of safety to more general concerns about fairness during competition and the diminution of what it means to be human. Some of these arguments may be used in the case of enhancement in the military, but the analogy between sport and

combat is an imperfect one. There are no “doping” rules in warfare since there is no requirement for battles to be fought on a level playing field beyond that which is stipulated in the international law of armed conflict. Indeed, performance enhancing drug-use in the military has been widely reported. The use of central nervous system stimulants in pilots to overcome fatigue, including by US pilots during the Vietnam war[26], the Gulf war[27], and the recent Afghanistan conflict is well documented with at least some chain of command approval.[28] Safety fears were highlighted after a friendly fire incident resulting in the death of four Canadian soldiers while the pilots had been taking dextroamphetamine.[29] Medical performance enhancement in the military environment thus shares with enhancement in sport concerns about risks and safety. Such concerns may be exacerbated by suspicions that it may have been utilised in secret, and without formal well-designed trials to assess safety and efficacy.[30] Other concerns around pharmacological enhancement include how prescription of medication for non-therapeutic purposes could affect the doctor-patient relationship and how regulatory and professional bodies would view this, including the use of medicines outside their licenced indication. For these reasons, additional ethical considerations are raised by type 2 LOB-ITs, and Mehlman *et al.* [6] provide a useful starting point (see Table 4) for exploring these. We are not proposing here the introduction of enhancement medicine for the purpose of enhancement. Rather, we are proposing that Type 2 LOB-ITs that fulfil all of the relevant ethical criteria (Tables 2-4) may be acceptable for use in combat *despite* their unintended but foreseen enhancing effects in circumstances of elevated risk. A LOB-IT intervention may be justified in one situation (high risk of trauma) without it automatically following that the same intervention would be justified in circumstances where intended effect was primarily that of enhancement.

Might enhancing interventions lead to an escalation of force?

The Geneva Convention (Chapter 4, Rule 14) stipulates that the principle of proportionality is adhered to when applying lethal force. If one side improves its defensive capability this may, in turn, justify larger and more destructive weapons being used by the other side as a proportionate measure. The use of LOB-IT could be perceived as an escalation of defensive capability by a belligerent party ultimately leading to a greater burden of suffering and harm than would otherwise have occurred. Whether physiological or anatomical enhancement of combatants might be used by an adversary to justify more destructive weaponry is not known, and has not been discussed in military doctrine or the military medical literature. It is unlikely that LOB-IT would be so effective as to justify escalation of force by a belligerent party. However, unfounded belief about the effectiveness of enhancement could potentially lead to use of greater force than would otherwise be justified if this belief was not operating. Such an escalation in the use of force may outweigh any benefits of the LOB-IT. This further highlights the importance of discussion to establish consensus as to the threshold of what constitutes an "enhancement" and what the justifiable military response to such an enhancement might be in terms of the Law of Armed Conflict.

Table 4 – Ethics of Medical Enhancement In A Military Context (Modified from Mehlman *et al.* 2013[6])

Legitimate Military Purpose	The enhancement must be used for legitimate military ends and the military purpose must be both legitimate and legal
Necessity	There must be no other way to achieve the desired outcome
Benefits Outweigh Risks	Benefits in this sense include those of the state, the unit, and the mission in addition to the individual involved. Risks include those to both combatants and civilians
Maintenance of Individual's Dignity	Enhancements that undermine the combatants dignity (e.g. through the induction of compromising appearance or behaviour) should be avoided
Minimisation of Burdens	The burden of the enhancement should be time-limited or reversible so that the combatant may return to civilian life with no lasting effects of the enhancement
Consent	As long as enhancement is considered an experimental process or carries "exceptional" risk, it should be given to combatants only with their informed consent
Transparency	As far as it is consistent with security considerations, information on military medical enhancement research and utilisation should be made available to the public or at least an independent third party in order to counter the negative perception of such research conducted in secret in the past
Fair Distribution of Risks and Benefits	Enhancements should be offered to combatants in a fair, rational, and justifiable way such that utility is maximised. Enhancements should not be allowed to confer unfair benefits such as increased performance in promotion or selection processes
Commanders are Accountable	Combatants must be protected from coercion and unethical or illegal use of enhancements. Commanders retain ultimate responsibility for the use of enhancement and any subsequent consequences that follow

CONCLUSION

We have outlined some of the ethical implications of left-of-bang interventions in trauma. We have suggested that Type 1 (purely prophylactic) interventions may be implemented in a similar manner to any experimental prophylaxis: that is to say, according to the ethical principles of medical research and prophylaxis use and taking into account the military context. Once the efficacy and risks of a LOB-IT are established, its use may be on a par with any other prophylactic interventions used by the military. In the case of Type 2 (prophylaxis with enhancement) interventions, additional ethical safeguards may be required due to its unintended side-effects. Our aim is start wider discussion with a view to achieving some consensus in the longer term regarding the delivery of “left of bang” interventions in future conflicts.

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