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Prophylactic anti-coagulation after severe burn injury in critical care settings

Megan Blake[1],

Ruth Roadley-Battin[2],

Tomasz Torlinski[2,*]

[1] *College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK*

[2] *Department of Anaesthetics and Intensive Care Medicine, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham, Birmingham, UK*

Background. Severely burnt patients are at an increased risk of thromboembolic complications, hence sufficient prophylactic anticoagulation is of paramount importance. Local guidelines at the Burns Centre in the Queen Elizabeth Hospital, Birmingham therefore advise increasing the standard dose of low molecular weight heparin in these patients. An audit was carried out to assess the current practice in burns patients to ensure adequate anticoagulation and adherence to guidelines.

Materials and methods. Retrospective data was collected on all burns patients in the Burns Centre over a two-year period. The main objectives were to assess:

- anticoagulation regimes prescribed to severe burns patients
- monitoring of Anti-Factor Xa levels
- adjustment of dosing based on the results

The locally produced trust guidelines were used as the comparator.

Results. All burns patients were prescribed anticoagulation, but often the dose was not increased as suggested in the guidelines. Although most of the severely burnt patients were prescribed adjusted higher doses of anti-coagulation, only 60% of these patients were monitored with Anti-Factor Xa assays. Of these assays, 66% showed sub-prophylactic levels. The majority of results led to the adjustment of the dose of anticoagulant. However, often dose changes were made late.

Discussion and conclusions. The audit confirmed the need for increased doses of prophylactic anticoagulation in severe burns. The better adherence to the guidelines can be achieved by additional training and implementation of decision support via electronic prescribing system.

Keywords: anticoagulation, thromboprophylaxis, burns, intensive care, heparin, Anti-Factor Xa, thermal trauma

* Correspondence to: Tomasz Torlinski, Department of Anaesthetics and Intensive Care Medicine, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS FT, Mindelsohn Way, Edgbaston, Birmingham B15 2GW, UK. Email: tomasz.torlinski@uhb.nhs.uk

BACKGROUND

Burns injuries are still causing a major burden on societies, leading to significant long-term morbidity with relatively high mortality (1). In spite of significant advances in health and safety, the trends showing decreasing prevalence, at least in the developed countries, are not consistent (2). The most current WHO Guidelines on Burns Prevention and Care indicate that mortality rates differ significantly from 11.6:100,000 population in South East Asia to around 1:100,000 population in Europe. Therefore burns injuries still constitute major workload for trauma services. In the UK, the most current analysis combining national databases TARNS and iBID, coming from trauma centres indicates that burns contributed to up to one in 20 severe traumas admitted in such centres with annual workload actually increasing (2). Therefore there is a continuous need for further advances in burns care.

In the UK, the median burn per total body surface area is only around 1.5% (iBID), which constitutes majority of patients (2). Other national dataset from Germany and the USA quote 10–30% of patients with burn injuries requiring admission to burns centres, inclusive of provision of critical care services, have significantly higher mortality and involvement of resources (3–5). The critical care of burns patients is multifactorial, taking into account the actual severity of acute burn, inhalational involvement, concurrent trauma and underlying medical problems, inclusive of frailty (5, 6). One of the complications related to severe trauma caused by burns is the hypercoagulable state (7). Although most typically the hypercoagulable condition presents itself during recovery phase, it is not unusual to encounter this in much early stages. The thrombotic complications are responsible for more than 3% death of all deaths in burns population (7). Therefore early establishment and monitoring of adequate prophylactic anticoagulation in the management of burns is of paramount importance. The data obtained from evaluation of burn services in German-speaking countries strongly supports usage of low molecular weight heparin, which leads to the reduction of thrombotic events and even further reduction in prevalence of heparin-induced thrombocytopenia (HIT syndrome) compared to the infusion of non-fractioned heparin (3).

Venous thromboembolism (VTE) prophylaxis strategies for the critically ill patients include the use of low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), or a newer direct acting oral anticoagulant (DOAC). Currently, DOAC use has no evidence in the critically ill population and therefore is beyond the scope of this article.

LMWHs such as enoxaparin have more predictable pharmacokinetic properties, reduced bleeding risk, and evidence of non-inferiority to UFH in treatment of VTE (8).

NICE VTE guidelines (9) recommend LMWH use in all critically ill patients where there are no contraindications and suitable adjustments to be made for renal dysfunction if required. However, previous trials have shown inadequate Anti-Xa response in critically unwell patients, including those with acute burns (10, 11). The clinical implication of this subtherapeutic response in terms of VTE diagnoses is unclear (12).

Enoxaparin in non-critically ill patients has a subcutaneous bioavailability of close to 100% (13). In the severely ill burn patients the pharmacokinetics of enoxaparin can be predicted to change due to intravascular hypovolaemia from fluid shifts, peripheral vasoconstriction, and initial augmented renal clearance (14). All of these factors make dosing in this patient group more difficult to predict. Our unit protocol for severe burn patients is therefore to give an increased dose of thromboprophylaxis from admission: enoxaparin 40 mg twice daily. Although monitoring is not routinely required for LMWH use, as described previously, the predictability in burns patients is not well established and therefore monitoring is undertaken four hours post third dose to achieve an Anti-factor Xa level of 0.1–0.3 IU/ml, which is adequate for thromboprophylaxis.

Clinical governance is the framework used in the UK by the NHS for continually improving the quality of services to maintain a high level of care (15). This is an umbrella term that encompasses factors including education, risk management, research, and clinical audit (16). It must be noted that there is a fundamental difference between research and audit. The former aims to find out what care, based on the new evidence, should be given in the first place. Audits, on the other hand, play a central role in monitoring clinical

practice by judging current care and highlighting areas of improvement, which ensures that patient treatment is optimised (17). Auditors measure care against defined standards, mainly national or local guidelines, to assess whether the set standards are being met in current clinical practice (16). Audit is based upon a five-stage cycle; this includes the identification of a problem, selecting criteria for audit review, measuring the level of performance, making improvement and sustaining positive changes (18). Therefore audits are part of a continuous quality improvement process, and further re-auditing ensures that the initial results are acted upon.

Therefore we have carried out an audit on the prophylactic anticoagulation of severe burns patients at the Burns Centre at the Queen Elizabeth (QE) Hospital, University Hospitals Birmingham NHS FT. The aim was to assess whether severely burnt patients were receiving the appropriate anticoagulation as per standard, and hence to decrease the risk of burns patients suffering from thromboembolic events. The comparator used was the locally approved guidelines.

MATERIALS AND METHODS

The method was based on the five-stage audit cycle (18). It was noted that there were inconsistencies in the anticoagulation prescribed to patients at the Burns Unit at the Queen Elizabeth Hospital, Birmingham, making it beneficial to audit current clinical practice.

The audit standards were the local trust guidelines at the Burns Centre located in the hospital.

These guidelines (19) advise that an increased prophylactic dose of low-molecular-weight heparin should be given to severely burnt patients. During the time period of this audit, the LMWH used in the QE Hospital was enoxaparin; it was therefore advised that severely burnt patients should receive Enoxaparin sc 40 mg BD. The LMWH given should be monitored with Anti-Factor Xa assays. These should be taken after the third dose, and this repeated weekly if no change in dosing. If the dose changes, the previous sending pattern should be followed until the prophylactic level is achieved (19).

There were three key objectives under investigation:

1. How are patients in critical care anti-coagulated and does this follow the guidelines?

2. Is anticoagulation monitored in the correct way according to the guidelines?

3. When Anti-factor Xa assays are taken, what are the results of this monitoring and are dose adjustments made?

The audit cohort included all patients admitted to the Burns Unit over a two-year period from April 2015 to March 2017. Exclusion criteria included death on the day of admission or pre-existing medical conditions affecting the anticoagulation prescribed. Retrospective data was collected for all of these patients from the QE Hospital electronic system, PICS. The audit was registered and approved by University Hospitals Birmingham NHS FT Clinical Audit Registration and Management System (project number: CARMS-1392).

The cohort of patients was divided into groups according to the burn severity, classified by TBSA% burn. The group with the lower severity of burns in this audit was defined as having 20% or less TBSA burns and the higher severity group had over 20% TBSA burns, with or without inhalational component. Birmingham Burns Centre guidelines were written specifically with regard to the latter group of burns patients, stipulating the increased dose of anticoagulation and monitoring with Anti-Factor Xa assays.

Data was collected for each patient. This included:

- Patient demographics
- Total body surface area (TBSA) burn percentage
- The initial dose of anticoagulation prescribed
- Whether Anti-Factor Xa assays were taken and if so, when were these assays taken
- Results of Anti-Factor Xa assays
- Action taken following Anti-Factor Xa assays.

According to the guidelines (19), monitoring should occur 4 hours after the third dose, hence if patients were in critical care for less than 30 hours, this would not have allowed sufficient time for Anti-Factor Xa assays to be taken. Therefore, in the assessment of whether monitoring occurred, further patients were excluded if they were not in critical care for a long enough period for this to have taken place.

The analysis of the data was carried out by comparing the care that the patients received to the standard, the trust guidelines.

RESULTS

In total, there were 48 patients admitted to the Burns Unit during the two-year study period and hence initially included in this audit. Seven of these patients were excluded due to either death on the day of admission or pre-existing medical conditions affecting the anticoagulation prescribed.

Of the remaining 41 patients included in this audit, 17 of these had suffered severe burns of over 20%, with the remaining 24 patients with less severe burns of TBSA burn of 20% or less. The study population consisted of mostly male patients (80%), with the mean age of the cohort being 46 years old (range 17–84). The majority of the burns were dry burns (83%), whilst the remainder had either chemical or electrical burns.

Every patient on admission to critical care was initially commenced on enoxaparin but of differing doses. Out of the 17 patients with over 20% TBSA burns, 11 of these were initially prescribed enoxaparin sc 40 mg BD as advised in the guidelines, whereas six patients were not treated as according to the guidelines and consequently only received enoxaparin sc 40 mg OD.

In the group of patients with 20% or less TBSA burn, one-third of the cohort received enoxaparin sc 40 mg BD, with the remainder receiving enoxaparin sc 40mg OD. As this group is not classified as severely burnt, the guidelines do not state that these patients require the additional anticoagulation, however, a large proportion still received the increased dose.

Five patients from the severely burnt group were excluded when assessing whether Anti-Factor Xa assays were taken, due to being in critical care for less than 30 hours. Out of the 12 remaining patients in this group, seven were monitored with Anti-Factor Xa assays. In the group of patients with 20% or less TBSA burn, only 10% were monitored with Anti-Factor Xa assays.

The Anti-Factor Xa assays showed a wide range of results. In total, 12 patients were monitored. Of these 12 patients, eight were found to have anticoagulation levels below the prophylactic range, two were above the prophylactic range, leaving only two patients with levels of anticoagulation within the required range.

It was found that out of the ten patients who were receiving a suboptimal dose of anticoagulation, half of them had dose adjustments made

Table 1. Patient demographics

		Patients with 20% TBSA burn or less	Patients with over 20% TBSA burn
Number of patients		**24**	**17**
Age when burnt	Mean (years)	50	41
	Range (years)	23–74	17–84
Number of patients of each sex	Male	22	11
	Female	2	6
Number of patients with each type of burn	Dry	19	15
	Chemical	3	1
	Electrical	2	1

Table 2. Anticoagulation prescribed

	Enoxaparin 40 mg OD	Enoxaparin 40 mg BD
Over 20% TBSA burns	6	11
Less than 20% TBSA burns	16	8

Table 3. Results of Anti-Factor Xa assays

	Sub-prophylactic	Within prophylactic range	Above prophylactic range
Number of patients	8	2	2

Table 4. Action taken following Anti-Factor Xa assays

	Dose adjustments within 24 hours	Dose adjustments after 24 hours	No action taken
Number of patients	5	4	1

within 24 hours. However, four of the patients' anticoagulation doses were not adjusted for over 24 hours, with one patient waiting six days before dose adjustments were made leaving them in a sub-prophylactic state for longer period of time. Finally, there was one patient who assayed with inappropriate anticoagulation levels but no action was taken to change the dose.

DISCUSSION

Venous thromboembolism (VTE) is a leading cause of morbidity, mortality, and prolonged hospitalization for inpatients. Common to other hospitalized patients, burn sufferers have an increased risk of VTE due to immobilization, trauma, major surgery, and indwelling vascular access devices. Virchow's triad describes the three elements which contribute to thrombosis risk- hypercoagulability, stasis of blood flow, and endothelial injury (20). In addition to the above risk factors burns patients may exhibit altered coagulability. One study from 2013 demonstrated that burn patients have normal coagulation parameters on admission yet within one week of injury may become hypercoagulable thereby increasing the VTE risk throughout admission (20).

The pathophysiological changes that occur as a result of burn injury may change the pharmacokinetic parameters of drugs. Enoxaparin in healthy subjects has a volume of distribution (Vd) equivalent to plasma volume and is metabolized to lower potency metabolites which are 40% renal excreted (13). A loss in capillary wall integrity in burns sufferers leads to early fluid (and electrolyte and protein) shifts into the interstitium, resulting in the loss of circulating plasma volume, tissue oedema, and reduced urine output (21). This results in an increased volume of distribution and reduced clearance of LMWH. After the acute phase, burns patients become hyperdynamic with increased cardiac output leading to enhanced hepatic and renal clearance of some drugs. Finally, altered peripheral perfusion and tissue oedema may reduce the subcutaneous bioavailability of enoxaparin. Anti-Factor Xa levels have previously been shown to be subtherapeutic in this population (11). All these factors necessitate dose adjustment to avoid increased VTE events and dose adjustments have previously been shown to be safe and efficacious (22).

This audit has revealed that over 60% of the Anti-Xa levels taken were sub-prophylactic despite the guidelines suggesting dose increases and regular monitoring. Dose increases of 25% or greater were required to achieve appropriate prophylactic Anti Xa levels in some patients. Therefore even regimes including adjusted thromboprophylaxis doses on admission require ongoing monitoring and dosage review due to the unpredictable pharmacokinetic changes that may occur.

In our audit we have found inconsistences in the dose of anticoagulation prescribed to burns patients. This is supported by the findings that not all severely burnt patients received a twice daily dose of enoxaparin despite guideline recommendations, with nearly half of patients not being monitored with Anti-Factor Xa assays. Moreover, considering the majority of patients receiving a double dose of LMWH were still inadequately anti-coagulated according to the assay results, it may suggests that those receiving only a once daily dose of anticoagulation will not be receiving adequate anticoagulation. Amongst the patients in the lower severity burns group, a third received enoxaparin twice daily despite the increased dose not being advised for this group. It is likely that prescribers are either unaware of the existence of the guidelines or are unsure of which burns patients to apply them to. Therefore clarification of which patients should be receiving enoxaparin twice daily instead of the standard once daily dose would be beneficial. Such clarification will be incorporated into the next revision of the guidelines. Similarly, the importance of the increased dose of anticoagulation in severely burnt patients is now emphasized to all new doctors commencing their posts in critical care by new regular

educational sessions and it is also included in ITU handbook.

The audit outcomes have highlighted the need for an increased awareness of the current guidelines amongst the staff at the Burns Centre, Birmingham to both allow for a standardised method of caring for burns patients, as well as minimizing the risk of burns patients suffering thromboembolic events. This is in terms of emphasising the importance of increased doses of enoxaparin in severely burnt patients and the monitoring of Anti-Factor Xa levels to ensure there is adequate anticoagulation. Medications at the Queen Elizabeth Hospital are prescribed using electronic prescribing systems. Despite these systems being beneficial, the standard dose of anticoagulation on the system is lower than what is advised for severe burns patients, making it very easy for doctors to automatically prescribe the lower dose. Therefore it relies on doctors adjusting the dose of LMWH from the standard dose, which is appropriate for most of inpatients. Addition of decision support including standardized order sets to computerized physician orders has been predicted to reduce the average hospital length of stay by 10% (23) as well as reducing adverse drug events by up to 90% (24). A decision support tool ensuring that prescribers are aware of the increased dose of anticoagulation in severe burns, or a sophisticated system that suggested dose alternations based on Anti Xa assay results, could be used improve the consistency in VTE prophylaxis prescribing in the future.

For these audit findings to be applied at a larger scale, it would be worthwhile for the anticoagulation practice in other burns centres internationally to be audited in a similar way to ensure that all severely burnt patients are receiving adequate anticoagulation.

Already following this audit, the results have been presented at a number of events to increase knowledge of the outcomes. This has included a presentation at Birmingham University Medical School, and more significantly, audit results have been presented at a national Burns Mortality and Morbidity meeting in the UK, and at Baltanest, an international conference of anaesthesiology, intensive care, and pain management.

CONCLUSIONS

The audit of prophylactic anticoagulation in severe burns confirmed the requirement of increased dosage of low-molecular-weight heparin in this population. The monitoring of the effectiveness of such treatment could be achieved by measuring Anti-Factor Xa level activity. The better adherence to the guidelines can be achieved by additional training and implementation of decision support via electronic prescribing system. Further studies are warranted to establish the most appropriate clinical approach to the hypercoagulable state encountered in severe burns treated in critical care.

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References

1. Smolle C, Cambiaso-Daniel J, Forbes AA, Wurzer P, Hundeshagen G, Branski LK, et al. Recent trends in burn epidemiology worldwide: a systematic review. Burns. 2017; 43(2): 249–57.
2. Stylianou N, Buchan I, Dunn KW. A review of the international Burn Injury Database (iBID) for England and Wales: descriptive analysis of burn injuries 2003–2011. BMJ Open. 2015; 5(2).
3. Busche MN, Herold C, Krämer R, Knobloch K, Vogt PM, Rennekampff HO. Evaluation of Prophylactic Anticoagulation, Deep Venous Thrombosis, and Heparin-Induced Thrombocytopenia in 21 Burn Centres in Germany, Austria, and Switzerland. Ann Plast Surg. 2011; 67(1): 17–24.
4. Burn Incidence and Treatment in the United States (American Burns Association - Internet resources) (accessed 2019 Jan 02) Available from: http://ameriburn.org/who-we-are/media/burn-incidence-fact-sheet/
5. McIntire AM, Harris SA, Whitten JA, Fritschle-Hilliard AC, Foster DR, Sood R et al.; Outcomes following the use of nebulized heparin for inhalation injury (HIHI Study). J Burn Care Res. 2017; 38: 45–52.
6. Ward J, Phillips G, Radotra I, Smailes S, Dziewulski P, Zhang J, et al. Frailty: an independent predictor of burns mortality following in-patient admission. Burns. 2018; 44(8): 1895–902.

7. Barret JP, Dziewulski PG. Complications of the hypercoagulable status in burn injury. Burns. 2006; 32(8): 1005–8.
8. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001; 134(3): 191–202.
9. National Institute for Health and Care Excellence. 2018. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NG89. Manchester: National Institute for Health and Care Excellence. [Online] [accessed 4 Jan 2019] https://www.nice.org.uk/guidance/ng89/chapter/Recommendations
10. Robinson S, Zincuk A, Strøm T, Larsen TB, Rasmussen B, Toft P. Enoxaparin, effective dosage for intensive care patients: double-blinded, randomised clinical trial. Crit Care. 2010; 14(2): R41.
11. Lin H, Faraklas I, Cochran A, Saffle J. Enoxaparin and Antifactor Xa levels in acute burn patients. J Burn Care Res. 2011; 32: 1–5.
12. Vahtera A, Vaara S, Pettilä V, Kuitunen A. Plasma anti-FXa level as a surrogate marker of the adequacy of thromboprophylaxis in critically ill patients: A systematic review. Throm Res 2016; 139: 10.
13. (The electronic Medicines Compendium (eMC) (eMC- Internet resources) (accessed 13 Jan 2019) available from: https://www.medicines.org.uk/emc/product/1695/smpc
14. Blanchet B , Jullien V, Vinsonneau C, Tod M. Influence of Burns on Pharmacokinetics and Pharmacodynamics of Drugs Used in the Care of Burn Patients. Clinical Pharmacokinetics. 2008; 47(10): 635–54.
15. Scally G, Donaldson LJ. Clinical governance and the drive for quality improvement in the new NHS in England. BMJ 1998; 317: 61–65.
16. Scrivener R, Morrell C, Baker R, Redsell S, Shaw E, Stevenson K, et al. Principles for the Best Practice in Clinical Audit. Radcliffe Medial Press. 2002.
17. Defining Research. National Research Ethics Service, National Patient Safety Agency, NHS. 2009.
18. Benjamin A. Audit: how to do it in practice. The BMJ. 2008; 336: 1242–5.
19. England K, Torlinski T, Roadley-Battin R. Guidelines for Management of Burns patients admitted to Critical Care at QEHB. Policy CG 139; version 2.1: issued 08/2017. University Hospitals Birmingham.
20. Van Haren, Thorson, Valle EJ, Busko AM, Guarch GA, Andrews DM, et al. Hypercoagulability after burn injury. Trauma Acute Care Surg. 2013; 75(1): 37–43.
21. Latenser B. Critical Care of the burn patient: the first 48 hours. Crit Care Med 2009; 37(10): 2819.
22. Lin H, Faraklas I, Saffle J, Cochran A. Enoxaparin dose adjustment is associated with low incidence of venous thromboembolic events in acute burn patients. J Trauma. 2011; 71: 1557.
23. Thompson DI, Classen DC, Haug PJ. EMRs in the fourth stage: The future of electronic medical records based on the experience at intermountain health care. JHIM 2007; 21(3): 49.
24. Delgado Sánchez O, Escrivá Torralva A, Vilanova Boltó M, Serrano López de las Hazas J, Crespí Monjo M, Pinteño Blanco M, et al. Comparative study of errors in electronic versus manual prescription. Farm Hosp. 2005; 29(4): 228.

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PROFILAKTINĖ ANTIKOAGULIACIJA PO SUNKIŲ NUDEGIMŲ INTENSYVIOS PRIEŽIŪROS SĄLYGOMIS

Santrauka

Įvadas. Pacientams, patyrusiems sunkių nudegimų, yra padidėjusi tromboembolinių komplikacijų rizika, todėl ypač svarbus profilaktinis antikoaguliavimas. Birmingemo Karalienės Elžbietos ligoninės Nudegimų centro vietinės rekomendacijos šiems pacientams siūlo padidinti standartinės mažos molekulinės masės heparino dozę. Buvo atliktas tyrimas siekiant įvertinti dabartinę praktiką dėl pacientų, patyrusių nudegimų, gydymo, siekiant užtikrinti tinkamą antikoaguliaciją ir rekomendacijų laikymąsi.

Medžiagos ir metodai. Dvejus metus buvo renkami retrospektyvūs duomenys apie visus Nudegimų centro pacientus, patyrusius nudegimų. Pagrindiniai tyrimo tikslai buvo įvertinti: pacientams skiriamą antikoaguliaciją, Xa faktoriaus lygių stebėjimą, dozavimo reguliavimą pagal gydymo rezultatus.

Rezultatai. Visiems pacientams, patyrusiems nudegimų, buvo skirta antikoaguliacija, tačiau dažnai dozė nebuvo padidinta, kaip nurodyta rekomendacijose. Nors daugeliui nudegimų patyrusių pacientų buvo nustatytos koreguotos didesnės antikoaguliacijos dozės, tik 60 % šių pacientų buvo stebimi pasitelkiant antifaktoriaus Xa tyrimus. 66 % šių tyrimų parodė, kad jie buvo profilaktiniai. Dauguma rezultatų paskatino koreguoti antikoagulianto dozes. Tačiau dažnai dozės keitimas buvo pavėluotas.

Diskusija ir išvados. Tyrimo rezultatai patvirtino, kad sunkių nudegimų gydymui reikia didesnės profilaktinės antikoaguliacijos dozės. Efektyvesnį rekomendacijų laikymąsi galima pasiekti skiriant papildomą finansavimą ir keičiant tvarką dėl elektroninės receptų sistemos.

Raktažodžiai: antikoaguliacija, tromboprofilaktika, nudegimai, intensyvi priežiūra, heparinas, terminė trauma