

Case Report

Intraoperative low molecular weight heparin and postoperative bleeding

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Accepted 16 March, 2020

A case of postoperative bleeding associated with low molecular weight heparin (LMWH) administration is reported. A literature search suggests that perioperative bleeding can be as high as 11% when LMWH is administered intraoperatively. When administered 6 h postoperatively, LMWH does not significantly increase the risk of bleeding whilst retaining efficacy for venous thromboembolism prophylaxis. Although LMWH has not been shown to be superior when compared to unfractionated heparin for general surgery, advantages include no need for monitoring and once daily dosage. During an acute bleeding episode, bedside functional monitoring (e.g. thromboelastography) is appropriate rather than anti-Xa levels. To reverse LMWH, use protamine first to reverse its effects partially, followed by replenishing factor X and II with FFP/Prothrombinex. If bleeding continues, consider using activated factor VIIa.

Key words: Heparin, postoperative bleeding, venous thromboembolism

Case report

A 45 kg 20 year old lady presented for removal of a pelvic tumour by a vascular surgeon. She had a 3 month history of worsening back pain which radiated down both her legs and into her feet. CT scan showed a well defined hypodense homogeneous mass adjacent and anterior to the L5 vertebral body, indenting the right psoas muscle.

This mass was 37 × 45 mm in size and 59 mm in length, and lay below the confluence of the iliac veins, displacing the right common iliac artery and vein anterolaterally. A PET scan did not show major uptake and no secondary deposits were visualised. She was taking tramadol PRN for her pelvic pain, had not received any chemotherapy or radiotherapy, and had been investigated in the recent past for pyrexia of unknown origin ultimately thought to be tumour related.

Her medical history included eosinophilic oesophagitis and occasional symptomatic reflux for which she was taking pantoprazole. Her previous gastroscopy and colonoscopy under general anaesthesia was complicated by postoperative nausea and vomiting. She also suffered from depression/anxiety and was on Lexapro (escitalopram), as well as an oral contraceptive pill. She was also on weekly intramuscular vitamin B12 injections for deficiency. Of note she had no prior history of easy bleeding or bruising. She consumed 8 standard drinks of alcohol

on the weekends but did not smoke. Cardio-respiratory and airway examinations were normal. She was sensitive to erythromycin, Rulide (roxithromycin) and Keflex (cephalexin), which made her itchy and nauseous. Her full blood count, electrolytes, urea, creatinine and liver function tests were normal.

She was the first case in the morning, and had graduated compression stockings (GCS) and intermittent pneumatic calf pumps (ICP) applied preoperatively. After inserting an intravenous (IV) luer, she was sedated with 2 mg midazolam and an epidural was inserted into the L3/4 interspace. General anaesthesia was induced with IV propofol/fentanyl/rocuronium, and cephazolin was given without sequelae. An arterial line and central line were inserted post-induction. She was maintained with desflurane/air/oxygen, 4 mg morphine IV and 7 + 5 ml 0.25% bupivacaine and 100 mcg of fentanyl was given into her epidural.

An hour into the operation, after having been satisfied with the haemostasis of the operative field, the vascular surgeon requested Fragmin (dalteparin) to be given subcutaneously for DVT prophylaxis. A discussion ensued regarding the correct dosing for her weight, and in the end 2,500 units were given over her deltoid subcutaneously. There was a pause intraoperatively to wait for

the result of Para aortic lymph node fresh frozen section, and further haemostasis was observed to be adequate. The frozen section (and subsequent confirmation) showed that the tumour was a Schwannoma (neurilemmoma), with no evidence of malignancy. Blood loss was minimal, and did not reach the suction bottle for the whole 2 h of the operation.

She was kept normothermic and was given dexamethasone and granisetron for nausea and vomiting prophylaxis. Towards the end she was given 1 g paracetamol and 40 mg parecoxib IV. Muscle relaxation was reversed with neostigmine and glycopyrrolate, and she was extubated uneventfully. For IV fluids she only received a litre of Compound Sodium Lactate and was started on 500 mls of Voluven 6% when she reached Post-Anaesthetic Care Unit (PACU).

She stayed in PACU initially due to inadequately controlled pain from a high midline incision, which the epidural did not cover. She was then given a 0.2% ropivacaine infusion at 10 ml/h into the epidural, and commenced on PCA morphine following the standard PACU morphine protocol at our institution. She also received 2 boluses of ketamine after which she became drowsy, but her pain was still difficult to control subjectively. After 4 h in PACU she became hypotensive and transiently tachycardic with low urine output, which resolved with boluses of crystalloid and colloid. She was reviewed at 6 h and found to be pale and tachycardic. A bedside Haemacue performed showed a haemoglobin level of 60 g/L. So she was transfused 2 units of packed red blood cells and the surgeons were informed.

After 8 h in PACU, she was taken back to theatre for re-laparotomy to stop the bleeding. A large pelvic haematoma was evacuated and no surgical cause of the bleeding was identified. The patient appeared to be very coagulopathic with multiple bleeding points and generalised ooze. The initial INR was 1.7; the APTT, 47 s (normal 28 - 42); fibrinogen, 1.0 g/L; Hb 64 g/L and the K^+ , 6.3 mmol/l. The surgical staff reported this as resembling disseminated intravascular coagulopathy (DIC) to the haematologist. Subsequent D-dimer levels were 0.2 initially and rose to 0.5 later that night when the coagulation was corrected (normal <0.3 mg/l).

The on-call anaesthetist had performed a rapid sequence induction supported with boluses of metaraminol. The haematologist consulted via telephone recommended Prothrombinex 2,500 units, DDAVP 14 mcg and calcium chloride 10% 10 mls, which were given during the operation. Neither the haematologist nor the on call anaesthetist was aware of the intraoperative Fragmin that was given during the initial operation. The patient required an additional 5 units of packed cells, 2 units of FFP, 10 units of cryoprecipitate and 2 pooled units of platelets intraoperatively. Her temperature dropped to 35.4°C by the end but her acid-base status remained normal throughout. She lost around 1250 ml of blood collected into the cell saver, of which 300ml was washed and given to the an-

aesthetist. However, he did not return the blood to her due to concern about the possibility of returning anticoagulated blood to the patient.

After the operation, the patient was transferred to ICU intubated with the epidural left unmanipulated. In ICU she received 950 mg tranexamic acid, 1 unit of packed cells and extra fluid boluses. Her coagulation profile normalised during the evening. She was extubated the following morning without sequelae and was later transferred to the general ward that day. Her epidural was removed 2 days later with a normal coagulation profile and her pain was controlled with PCA morphine, ketamine, paracetamol, celecoxib and oxycodone. She was recommenced on DVT prophylaxis of subcutaneous Fragmin 5,000 units the next day and the dose cut to 2,500 units 5 days later due to a small vaginal bleed. She was discharged 8 days after her initial surgery.

DISCUSSION

This case illustrates a very important, but often neglected association with post-operative bleeding, which is the administration of low molecular weight heparin (LMWH). A few important questions remain to be answered in this case report.

- i.) Is this bleeding caused by LMWH? If so what is the risk of bleeding with LMWH?
- ii.) What is the efficacy of LMWH? Should LMWH be given in this case?
- iii.) Are all LMWH the same? How is dalteparin different?
- iv.) If administered, how should we give dalteparin?
- v.) How should we monitor and treat this patient with acute bleeding?

A simple Medline search of the keywords including LMWH/dalteparin in combination with bleeding, general surgery, efficacy, monitoring and reversal is performed. As the information on LMWH and venous thromboembolism (VTE) is extensive, only those pertaining to this case will be presented. A few of these issues are interrelated and will be repeatedly discussed in their respective sections.

Is the bleeding caused by LMWH? What is the risk of bleeding from LMWH?

All other potential causes for bleeding in this case are likely to have contributed only trivially to the blood loss. Eosinophilic oesophagitis is not associated with coagulopathy (Swoger et al., 2007; Furuta et al., 2007; Blanchard et al., 2006), except for haematemesis from oesophageal reflux. Intraintestinal Schwannoma is only associated with intraluminal bleeding and not coagulopathy (Tong et al., 2003). The use of parecoxib alone does not cause coagulopathy (Noveck et al., 2001), but combining other non-steroidal anti-inflammatory drugs with LMWH has been

associated with significant bleeding (Greer et al., 1999). OCP use is associated with increased risk of VTE, not coagulopathy (Norris and Bonnar, 1997).

The colloid provided intraoperatively, namely Voluven 6%, was unlikely in this case to cause significant coagulopathy in the volume administered (Gandhi et al., 2007; Langeron et al., 2001; Standl et al., 2008). Postoperative Gelofusine could have potentially caused a dilution coagulopathy (Barron et al., 2004); however it was used to treat hypotension and tachycardia resulting from prior significant bleeding. The only other possible contributor was escitalopram, a selective serotonin reuptake inhibitor (SSRI), which has been shown to impair platelet function (Serebruany, 2006). However, if this was the case, it would have manifested during the initial surgery. Interestingly she was never informed of the possibility of serotonergic syndrome when combining Tramadol with escitalopram (Chinniah et al., 2008; Kam and Chang, 1997). Although she was vitamin B12 deficient, she did not exhibit any form of anorexia, nor was there any indication of vitamin K deficiency as her liver function tests were normal.

Although at the time of the second operation "no surgical cause of bleeding was found", we postulate it is likely that there was an initial bleed which was compounded by the action of dalteparin. Although dalteparin by itself can cause retroperitoneal bleeding without surgery, it is a very rare event (Porrás et al., 2001). Subsequent blood tests showed a consumptive coagulopathy, and not a DIC picture as reported by the surgeons (Taylor et al., 2001). Dalteparin is actually used for the treatment of DIC (Cummins et al., 2001; Miyake et al., 2001), and in fact may decrease the incidence chronic DIC (Cummins et al., 2001).

So what is the risk of bleeding?

This is the central issue of safety for LMWH administration. The answer would depend on how much, and when LMWH is given (Geerts et al., 2008; Mismetti et al., 2001; Smith and Canton, 2003; Gutt et al., 2005). Haemorrhage was, as expected more pronounced with LMWH compared to placebo, with an increase of 103% for major haemorrhage (2.8% prevalence), 106% for total haemorrhage, 88% for wound haematoma and 53% for the number of patients requiring postoperative transfusion (Mismetti et al., 2001). Due to the efficacy of LMWH at reducing VTE, subsequent studies were conducted comparing with UFH. Therefore any discussion of recent data without comparing with UFH on all topics discussed here is irrational.

The accepted timing of low dose unfractionated heparin (UFH) was established as being 2 h preoperatively in the 1970s and in the 1980, when LMWH was introduced, a dose of 5000 IU 2 h preoperatively was used. The risk of bleeding was reported as high (11.6% LMWH vs 4.6% UFH) (Bergqvist et al., 1986). Excessive bleeding was also reported when the first dose was lowered to 2500 IU (Raskob and Hirsh, 2003), being as high as 5.9% in one

study (Kakkar et al., 1993). Subsequent studies have abandoned doses closer to the operation, and the rates of bleeding are reported between 2.4 - 4.7% (Bergqvist et al., 1995; Thomas, 1997), with the rate of major bleeding in patients treated up to 10 days reported between 0.8 - 2.4% (Gouin-Thibault et al., 2005).

Whilst a higher dose of LMWH confers a lower VTE rate compared to UFH, it comes with a cost of higher bleeding risk (Bergqvist et al., 1995; Holzheimer, 2004; Tribout, 2007). Data from newer thromboprophylactic drugs such as fondaparinux and ximelagatran show the risk of major bleeding is greatest when administered 2 h preoperatively, with the odds ratio normalising when administered 9 h postoperatively (Tribout Colin-Mercier, 2007). However, coupled with the thromboprophylactic efficacy, a dose of 12h preoperatively or 6 h postoperatively would seem appropriate, especially if regional anaesthesia is considered (Bergqvist et al., 1995; Tribout Colin-Mercier, 2007).

What is the efficacy of LMWH? Should LMWH be given in this case?

Since the population of patients undergoing general surgery is quite heterogeneous, the precise risk of this case cannot be derived from known figures generated by research. The Thromboembolic Risk Factors (THRIFT-II) Consensus Group (Scurr et al., 1998) and the 7th American College of Chest Physicians (ACCP) for the prevention of thromboembolism (Geerts et al., 2004) estimate the risk in this case as somewhere between 10 - 20% calf and 2 - 4% proximal deep vein thrombosis (DVT), 1 - 2% clinical pulmonary embolism (PE) and 0.1 - 0.4% fatal PE. The 8th ACCP guidelines recently published give a blanket rate of 10 - 40%, although recommending formal risk assessment models for individualised risk estimation (Geerts et al., 2008).

One could argue that from population studies the risk was negligible at 20 years of age (Fowkes et al., 2003), assuming there are no silent thrombophilic disorders (Rosendaal, 1999). The 8th ACCP guidelines recognises that most studies they reviewed were done on patients >25 years of age (Geerts et al., 2008). However, to my knowledge no current published guidelines have stated the lowest acceptable age limit for thromboprophylaxis. Whilst most paediatric studies are below the age of 18 (Hofmann et al., 2001; Nohe et al., 1999), reporting a rate of VTE of 5.2/100,000 (Jackson and Morgan, 2008). The current paediatric guidelines stress the importance of risk factors such as cancer, obesity, oral contraceptive use and central line insertion (Monagle et al., 2008; Ho et al., 2004; Bergqvist, 2004), some of which are prevalent in this young lady.

How effective is administration of LMWH to decrease the incidence of VTE in general surgery?

A meta-analysis suggests that compared to no treatment

or placebo, LMWH significantly reduces DVT in the order of 72%, clinical PE is decreased by 75%, and clinical VTE decreased by 71% with a trend towards a reduction in overall mortality (Mismetti et al., 2001). It also argues that whilst a dose of <3400 IU is as effective as UFH, a dose of >3400 IU can further reduce VTE compared to UFH, at the cost of increased bleeding risk. A recent re-view also found similar conclusions, except that the studies included were too heterogeneous and no meta-analysis was performed (Bergqvist, 2004). An even more recent Cochrane review for colorectal surgery found a similar magnitude of decrease in VTE, although LMWH was again found to be as effective as UFH (Wille-Jørgensen et al., 2004).

Closer to home, the Australian National Health and Medical Research Council (NHMRC) has appointed the National Institute of Clinical Studies to help develop an evidence-based guideline for the prevention of VTE in hospitalised patients suitable for use in the Australian health care context (National Health and Medical Research Council, 2004).

This is what our hospital protocol is based on. This approach is comparable to international standards for reducing the risk of venous thromboembolism (National Institute for Health and Clinical Excellence, 2008).

At our hospital, we have recently included VTE prophylaxis into our 'time out' protocol to increase compliance. According to our protocol, this case had a high risk for VTE since it was major surgery (>45 min) and our patient was aged <60 years with one or more risk factors. The risk factors present in our protocol were oestrogen use (OCP), possible inflammatory bowel disease, and presumed malignancy. Other risk factors normally considered, but not present, were previous VTE, pregnancy or post-partum <1 month, obesity and presence of varicose veins. Prophylactic treatment for such a case would normally be subcutaneous dalteparin 5000 units 6 h postoperatively, and graduated compression stockings (intermittent pneumatic calf compressions may also be considered).

The obvious answer to the question of whether to administer LMWH is the balance between risk and benefit. However, with the paucity of data in this age group and weight, there is no way of making an informed decision.

There were no identifiable contraindications in this case. Falling back on our hospital protocol, it would seem reasonable to give dalteparin subcutaneously.

Are all LMWH the same? How is dalteparin different?

Low molecular weight heparin has been the cornerstone of venous thromboembolic event (VTE) prophylaxis since its introduction into the market (Weitz, 2006). Recently in our hospital, enoxaparin has been largely replaced by dalteparin, due to its cost and recent problems with over-sulphated chondroitin sulphate (<http://www.tga.gov.au/alerts/medicines/clexane.htm>). We

are more familiar with the use of enoxaparin but assume equal efficacy for VTE prophylaxis across the drug class (Weitz, 2006). Although there are few head-to-head clinical studies, bioequivalence of dalteparin and enoxaparin in anti-Xa activity has been shown in a small study (Eriksson et al., 1995).

Although heparin chains vary from 3000 to 30,000 Daltons (Da), LMWHs are derived from a variety of chemical or enzymatic cleavage techniques from heparin to produce unique structural alterations with a narrow range of molecular weights. Various pharmacopoeias describe LMWHs as products having an average weight less than 8000 Da, an anti-Xa potency of at least 70 International Units (IU)/mg, and a ratio of anti-Xa to anti-IIa activity of at least 1.5 (Jeske et al., 2008). Although LMWHs are characterised by anti-Xa activity, human and animal studies have failed to demonstrate a correlation with anti-thrombotic or haemorrhagic activity, which suggests a significant contribution by other mechanisms (Jeske et al., 2008). Other pharmacodynamic effects include thrombin activatable fibrinolysis inhibition, tissue factor pathway inhibition, minimal platelet factor 4 inhibition, various interactions with cells and proteins, and functional modulation of growth factors (Weitz, 2006; Jeske et al., 2008).

The pharmacokinetics of LMWHs is one of the reasons they are such attractive drugs to use. Neither monitoring nor dose adjustment is considered necessary due to their long half-lives (Weitz, 2006; Horlocker, 1997).

However, due to the advent of generic LMWH encroaching into the market, the issue of distinctiveness of individual LMWH has been hotly debated (Jeske et al., 2008; Leong and Hoppensteadt, 2003; Maddineni et al., 2006; Fareed et al., 2004; Fareed et al., 2005). It is shown that LMWH exhibits specific molecular and structural attributes determined by the type of manufacturing process used. Even generic versions with similar molecular and pharmacopoeial profiles have marked differences in their biological and pharmacological behaviour. Therefore, we should not measure every LMWH with the same yardstick and should consider each LMWH and their clinical trials individually.

Dalteparin is a LMWH derived from standard porcine UFH by partial nitrous acid polymerisation. It has a mean molecular weight of 5000 Da, with 90% of its chains falling between 2000 - 9000 Da (Bethesda et al., 1999). Its anti-Xa to anti-IIa activity ratio is 2.7, reflecting its anti-thrombotic effect versus its anti-IIa effect which may reflect its relative risk of bleeding (Weitz, 2006). The dose of dalteparin is thus expressed in units of anti-Xa activity relative to the First International Standards for Low Molecular Weight Heparins, the reference standard adopted by WHO in 1988 (Barrowcliffe et al., 2000). Since its inception in 1993 and approval by the FDA in 2000, multiple studies have proven its usefulness in VTE prophylaxis and treatment, treatment of coronary heart disease and anticoagulation for multiple purposes (Dunn and Jarvis, 2000).

If administered, how should we give dalteparin?

Issues to be considered here are the dose, timing, cessation and with relation to the epidural inserted.

Dosage

In this patient the suitable dose of dalteparin remains controversial. Initially most investigators compared dalteparin 2500 IU once daily with UFH 5000 IU twice daily, resulting in lower doses having been used in the past (Bethesda et al., 1999). However, subsequently, 5000 IU doses of dalteparin showed superiority over UFH 5000 IU 2 - 3 times daily, and all subsequent studies have moved to this dosing regime (Bethesda et al., 1999). Even with a preoperative dose the evening before surgery, dalteparin 5000 IU is more effective than 2500 IU (Bergqvist et al., 1995). A meta-analysis indicates that at doses below 3400 IU, LMWH is as effective as, and safer than, UFH, while at higher doses it yielded slightly higher efficacy but at the cost of increased haemorrhagic risk, including major haemorrhage (Mismetti et al., 2001). Nevertheless, in one study, 5000 IU was suggested as being inadequate for women undergoing surgery for gynaecological cancer (DeBernardo et al., 2005), which may have been the case before her histology result was reported.

On the other hand, could that dose of dalteparin be considered an overdose because she weighed only 45 kg? Judging from paediatric dosing, a routine prophylactic dose of 45 – 100 IU/kg results in anti-Xa activity between 0.2 and 0.4 IU/ml (Hofmann et al., 2001; Nohe et al., 1999; Monagle et al., 2008). By extension, this young lady should have received 2025 to 4500 IU of dalteparin.

The dose we administered was appropriate for her size, whereas the recommended 5000 IU of dalteparin would have been an over dosage. In our hospital we stock syringes of dalteparin in 2500 and 5000 IU sized vials.

However, the anti-Xa activity should theoretically still be monitored as there is considerable variation between lower weight individuals (Nohe et al., 1999; Ho et al., 2004).

Timing

The timing of intraoperative administration of LMWH is also controversial (Geerts et al., 2008; Mismetti et al., 2001; Raskob and Hirsh, 2003; Holzheimer, 2004). According to orthopaedic data (Raskob and Hirsh, 2003), which is the most extensively investigated subgroup, there is no difference in the efficacy of VTE prophylaxis when LMWH is administered preoperatively within the 2 h prior to surgery compared to 6 h postoperatively. In fact, comparing that 2 h period before surgery to 6 h postoperatively, the risk of bleeding increases without increasing VTE prophylaxis efficacy. The strongest evidence comes from the North American Fragmin Trial (NAFT) (Hull et

al., 2000), which indicated that a preoperative dose does not result in a clinically important improvement in effectiveness compared to the regimen administered 6 h postoperatively. Initiation of prophylaxis 12 - 24 h postoperatively may be less effective than 6 h postoperatively, which is considered to be the optimal timing for LMWH administration (Raskob and Hirsh, 2003).

Can this data be transferred to the general surgical population? There is no equivalent of the NAFT in general surgery to further elucidate this topic, whilst initial studies suggest comparable relative risks (Nurmohamed et al., 1992). However, the operating surgeons involved were vascular surgeons and they are accustomed to operating on fully heparinised patients while maintaining a low risk of bleeding. Moreover, the peak anti-Xa activity occurs 3 - 4 h after subcutaneous LMWH administration, and 12 h anti-Xa levels are approximately 50% of the peak levels (Horlocker, 1997). One could argue that, unlike vascular surgery, the heparin was not reversed with protamine at the end of this case, so the bleeding risk is bound to be higher than a vascular case.

Cessation of therapy

There is also controversy surrounding the cessation of therapy. Late thromboembolic complications after cessation of postoperative prophylaxis are known to occur up to 7 weeks after surgery. A number of trials have tried to examine whether prolonged thromboprophylaxis significantly reduces VTE rates in the general surgical population (Geerts et al., 2008). Although effective, LMWH was not found to be cost effective in a vigorously conducted economic analysis (National Institute for Health and Clinical Excellence, 2008). Other studies also support the notion that prolonged administration of LMWH does not seem to be justified in general surgery (Holzheimer, 2004). However, the cost-effectiveness of in hospital dalteparin administration vs UFH is supported by 2 studies (Heerey and Suri, 2005; Tzucs and Schramm, 1999), which show the dose of 5000 IU is even more cost-effective than 2500 IU (Nurmohamed et al., 1992). The 8th CAPP guidelines recommend in-hospital administration of LMWH of 10 days or more, until the patient leaves hospital in the general surgical population, except for cancer patients (Geerts et al., 2008).

In relation to epidural insertion, the American Society of Regional Anesthesia (ASRA) has published guidelines for regional anaesthesia in anticoagulated patients (Horlocker et al., 2003; Horlocker, 2008). Consideration should be given for omitting or delaying dalteparin dose when requested an hour into the case after an epidural has been inserted. ASRA recommends the administration of LMWH after 2 h post epidural insertion, but as the onset of peak action is later and the risk of bleeding is minimal, it was considered appropriate for intraoperative administration (Horlocker, 1997; Horlocker et al., 2003). Furthermore,

during vascular surgery, full heparinisation is acceptable 1 h into the case after epidural placement. For obvious reasons there are no randomised controlled trials on the subject, but recommendations exist (Horlocker, 2008; Rock, 2008). We should also take into consideration that the estimated VTE risk is usually less with an epidural than without (Ballantyne et al., 2005).

How should we monitor and treat this patient with acute bleeding?

Monitoring of LMWH administration is a matter of debate. The activated partial thromboplastin time (aPTT) is a relatively insensitive measure of LMWH activity. Anti-Xa level can be measured and it is a more sensitive measure of LMWH anticoagulant effect. This can be measured by clot-based essays (Heptest) or amidolytic assays (more sensitive) (Horlocker, 1997). Consensus guidelines recommend a chromogenic anti-Xa activity assay as a standard technique to monitor LMWH activity. However, one study showed that 3 different chromogenic methods do not give equivalent anti-Xa levels (Kovacs et al., 1999). Another paper suggests that LMWH dose should be adjusted to extrinsic coagulation activity assay (EXCA), which may emerge as a standardised test in the near future (Steif et al., 2006). In our hospital, we use a chromogenic technique called STA®-Rotachrom® Heparin, which has a turnaround time of half an hour.

To complicate things, normal therapeutic ranges are not clearly defined, and the timing of peak activity may not be clinically practical. For twice daily injections, the level should be determined 3 - 4 h after the third or fourth dose. But for once daily injections, the level should be determined 4 - 6 h after the second or third injection (Gouin-Thibault et al., 2005). As these laboratory tests are expensive, time consuming and the anti-Xa level is not predictive of bleeding, we do not routinely test for Xa activity after LMWH administration in our hospital. However, in this scenario there was a need for coagulation tests for therapeutic purposes. Furthermore, routine monitoring is advised in paediatric patients and adults weighing <50 kg, as well as patients with renal disease for dose adjustment (Weitz, 2006).

In the operative setting, a bedside test such as factor Xa-activated whole blood clotting time (Xa-ACT) or thromboelastography (TEG) would be more useful. Xa-ACT is a point-of-care test modifying the ACT test for heparin activity to suit LMWH monitoring. Instead of siliceous earth, bovine factor Xa is used as the activating agent, and is shown to be sensitive enough for monitoring LMWH *in vitro* as well as *in vivo* (Frank et al., 2004). TEG measures the dynamic process of blood coagulation based on viscoelastic properties. It has been shown to reduce blood product use in cardiac surgery when used perioperatively. When studied with LMWH anticoagulation, there appears to be a dose-dependent inhibition of TEG clotting even with minimally prolonged aPTT (Zmu-

da et al., 2000). However, our hospital does not possess these tests.

In this scenario where the patient was coagulopathic, the appropriate treatment should be a dose of protamine followed by topping up factor X and II levels. Although heparinase can reverse the effects of LMWH, we do not use it *in vivo*. A dose of 1 mg protamine/100 LMWH anti-Xa units reverses 90% of anti-IIa and 60% of anti-Xa activity⁴⁸. However, both anti-IIa and anti-Xa activity may return up to 3 h after protamine reversal, possibly due to release of additional LMWH from the subcutaneous depot (Horlocker, 1997). If coagulopathy persists, consider using activated factor VIIa (Novoseven). A report of 3 cases using a single bolus IV infusion of activated factor VIIa appears to have been effective (Firozvi et al., 2006).

Multiple drugs have been tried to reverse heparin instead of protamine, including recombinant platelet factor 4 (Mixon and Dehmer, 2004; Levy et al., 1995; Dehmer et al., 1995) and hexadimethrine (Kikura et al., 1996), but both products are unavailable to us. There are new treatments for the reversal of LMWH on the horizon, with peptides specifically engineered for this purpose. They contain series of peptides based on consensus heparin binding sequences, or a modification of them (Schick et al., 2004; Schick et al., 2001). They are alternatives to protamine in reversing unfractionated heparin, LMWH or danaparoid, without the undesirable effects of anaphylaxis and severe decreases in blood pressure and heart rate.

In summary, although controversy exists over whether dalteparin should be administered in this case, a conclusion is made that dalteparin administration is not unreasonable based on protocol. Unfractionated heparin twice or three times a day may be an alternative choice, which can be monitored with aPTT and reversed by protamine, but it is not in our protocol. One should be mindful of the risk of bleeding, and as such, dalteparin should be given 6 h postoperatively if no bleeding occurs. The subcutaneous dosage of dalteparin should be 2500 IU daily, taking into account the age, weight and risk of VTE vs bleeding in this patient. Although unavailable, 'near patient' functional monitoring like TEG should be considered. Better communication between all medical staff with regards to management of bleeding is a lesson to be learnt. To reverse LMWH, administer protamine to reverse LMWH effect partially, followed by FFP/Prothrombinex. Consider activated factor VIIa if bleeding persists. Good general care of patient to achieve normothermia, normal pH and normovolaemia is also very important.

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