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Original article

Delivery of low molecular weight heparin for prophylaxis against deep vein thrombosis using a novel, needle-less injection device (J-Tip®)

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Given daily, low molecular weight (LMW) heparins are established for prophylaxis against deep vein thrombosis (DVT). We describe delivery by a novel, needle-less device that is virtually painless in action. Its use could provide benefits for patients in terms of comfort both psychologically and physically, and for healthcare workers in terms of safety from needle-stick injury. Patients undergoing elective surgery received LMW heparin delivered subcutaneously by either a standard needle and syringe or by the needle-less injection device, J-Tip®. Pain was scored at the time of injection and plasma anti-factor Xa levels compared between the two methods of drug delivery 4 h later: 29 patients received LMW heparin delivered by the J-Tip® and 31 patients by standard needle and syringe. The J-Tip® was significantly more comfortable for the patient as the method of drug delivery (P <0.001). When delivered by the J-Tip®, LMW heparin was equally as efficacious, as plasma anti-factor Xa levels were similar for both methods of delivery (P <0.42). In summary, delivery of LMW heparin by the J-Tip® device was both comfortable and effective. These findings, taken in conjunction with its ease of use and complete freedom from risk of needle-stick injury might encourage further examination and use of this type of product.

Key words: Needle-less injection – Low-molecular weight heparin –Prophylaxis – Deep vein thrombosis – Randomised controlled trial.

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Low molecular weight (LMW) heparins are well established for prophylaxis against deep vein thrombosis (DVT) in patients undergoing various forms of elective surgery.[1-4] Notably, they have an improved pharmacokinetic bio-availability and plasma elimination half-life compared with unfractionated heparins, which enables them to be given subcutaneously as a single daily dose rather than the 8–12 h dosing regimens required for unfractionated heparins.[5,6]

Generally, measurement of plasma anti-factor Xa activity is accepted as the standard by which to assess the anti-coagulant activity of LMW heparins.[7,8] In this study, in order to provide routine prophylaxis against the formation of a postoperative DVT, we have used a novel, needle-less injection system (J-Tip®) in comparison with a standard, pre-filled needle and syringe to deliver subcutaneously, the LMW heparin Dalteparin sodium (Fragmin®, Pharmacia & Upjohn, UK). We measured first, the patients' perceived level of pain as experienced for each type of injection method used and, subsequently, the plasma levels of anti-factor Xa as a measure of the anti-coagulant activity of the LMW heparin once delivered.

Patients and Methods

The J-Tip® needle-less injection device

The J-Tip® needle-less injection device represents a novel, single-use, disposable device for the delivery of any liquid diagnostic or therapeutic agent directly into the subcutaneous space. It is regulatory body approved (US-FDA and EC-CE mark) and has been designed to be easy to use by both the patients themselves and all healthcare workers. The device (Fig. 1) is approximately 10 cm in length and weighs less than 9 g. Two sizes are available – 0.25 ml capacity and 0.5 ml capacity – and each device allows variable filling from 0.02 ml upwards. Medication delivery is under high pressure, created by release of carbon dioxide gas held in a small cartridge. This is achieved at high velocity, under high pressure (~3000 psi) and within a fraction of a second (~0.2 s). Specifically, the design enables delivery of medication that is virtually painless with penetration of the tissues to an approximate depth of 5–8 mm. Once used, the device can not be re-filled or re-used and is disposed of into an ordinary clinical waste system.

The J-Tip® device (i) should help eliminate the anxiety associated by some individuals with needles; (ii) has been designed such that no special skills are required to administer medication from it; (iii) is virtually painless in use; (iv) is unable to accidentally deliver medication intravenously; and (v) perhaps more fundamentally, eliminates the chance of needle-stick injury and significantly lowers the potential for cross-infection as no needles are used either in drawing up the medication or in its delivery.

Patients

Sixty patients, resident on surgical wards (at the Middlesex Hospital, London, UK) for more than three days and who were receiving subcutaneous LMW heparin (2500 IU/day) as prophylaxis against DVT, gave consent and were recruited into this study. The study design was a single-blind, randomised, controlled trial as agreed by the Local Research Ethics Committee (for University College Hospitals, London, UK). Specifically, a crossover design was not used to eliminate a potential bias in pain scoring; an individual's interpretation of pain could be biased according to the method of drug delivery received first.

Patients were randomised by coin-toss and received 2500 IU of Dalteparin sodium delivered subcutaneously in a total volume of 0.2 ml solution by either standard pre-filled needle and syringe or by a J-Tip®; sterile filled by the Pharmacy Department at the Middlesex Hospital, London, UK. Following the injection, pain was scored by each patient using a previously explained analogue system rated from '0' = no pain to '4' = very painful.

Methodology

Four hours following delivery of LMW heparin, any bruising at the site of injection was measured and recorded as the maximum width of the bruise in mm.

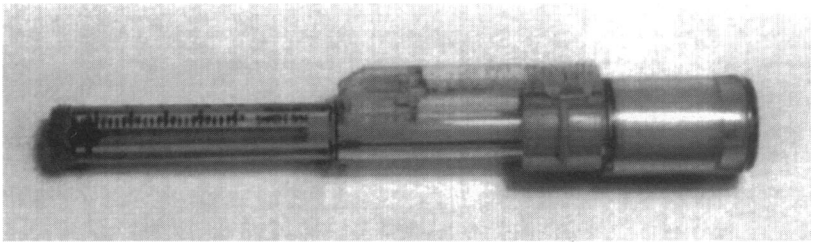

Figure 1 The J-Tip® needle-less injection system

Additionally, 5 ml of peripheral blood was collected by vein puncture into glass Vacutainer® tubes containing 0.109 M sodium citrate for plasma anti-factor Xa analysis (C_{max} Dalteparin sodium = 3.0–4.0 h).[6] Blood samples were centrifuged (3000 *g*, 15 min, 4°C) and the plasma stored frozen at –80°C. Analysis of plasma anti-factor Xa levels was performed according to standard protocols by the Haemostasis Department, University College Hospitals, London, UK.

For each patient (i) age; (ii) gender; (iii) pain score on injection; (iv) bruising at the site of injection; and (v) plasma anti-factor Xa levels were recorded to allow comparison between LMW heparin delivered by needle and syringe and by the J-Tip® device.

In analysis of the results, all subject variables were included if a value for plasma anti-factor Xa level was obtained. If, however, a subject required pain management treatment for clinical reasons prior to the injection, then the respective pain score only was eliminated from analysis.

Statistical analysis

Statistical analysis of gender distribution, age and pain score on injection was by the Mann and Whitney U-test or by Chi-square test, as appropriate. For comparisons of plasma anti-factor Xa, results were analysed first by a one-sample Kolmogorov-Smirnov test for normality and subsequently by Student's *t*-test, paired or unpaired as appropriate (all tests, two-tailed).

Results

Of the 60 patients recruited, 29 patients received LMW heparin delivered by the J-Tip® device: 18 males, 11 females with a median age of 70.5 years (range, 23–82 years). The remaining 31 patients received LMW heparin by standard needle and syringe: 18 males, 11 females with a median age of 69 years (range, 21–82 years); for 2 individuals, gender was not recorded.

In all comparisons within and between the J-Tip® and needle and syringe groups, no significant differences were observed with gender for distribution ($P > 0.1$, Chi-square), age or pain score (both $P > 0.1$, Mann and Whitney U-test), or plasma anti-factor Xa levels ($P > 0.1$, Student's unpaired *t*-test).

When comparing the pain scores from injection, the J-Tip® was significantly more comfortable for the patient, giving a median pain score of 0 (range, 0–2; $n = 28$) versus 2 (range, 0–3; $n = 18$) for the needle and syringe group ($P < 0.001$, Mann and Whitney U-test).

However, of perhaps greater importance, the J-Tip® was equally as effective at delivering the LMW heparin as a standard needle and syringe, as the levels of plasma anti-factor Xa measured in the peripheral blood of subjects following LMW heparin delivery were similar – mean ± SEM values for plasma anti-factor Xa of 0.154 ± 0.010 U/ml for the J-Tip® group ($n = 29$) versus 0.180 ± 0.030 U/ml for the needle and syringe group ($n = 28$); $P < 0.42$, Student's unpaired *t*-test.

Bruising at the site of injection was not observed as a problem with either the J-Tip® or needle and syringe as the method of LMW heparin delivery.

Discussion

The J-Tip® needle-less injection device has several potential benefits over a traditional needle and syringe for delivery of liquid therapeutic or diagnostic agents into the subcutaneous space. In particular, it should help eliminate anxiety induced by a fear of needles. This may be especially important for children. In this trial, although no patient expressed a particular fear of needles, it was the case for both men and women that the needle-less device was preferred and, significantly, pain scores were lower.

No special skills were required by the clinical and nursing staff to learn how to use the J-Tip® device, and training in its use took very little time. Using a technique of holding the J-Tip® perpendicular, pushed firmly against the skin and preferably where the subcutaneous layer is thickest (*e.g.* the abdominal wall or thigh), the device can deliver its medication virtually painlessly. The high velocity and high-pressure delivery of medication through a micro-orifice at the device tip delivers the liquid medication in an aerosol form to a depth of 5–8 mm, fanning out on maximum penetration to a width of approximately 8–10 mm. This allows the medication delivered to permeate through the subcutaneous space rather than being delivered as a liquid depot as would occur with a needle and syringe. Theoretically, this may enhance drug uptake and, in this trial, the slightly lower (although not significant) levels of anti-factor Xa seen in the plasma of patients after delivery by the J-Tip® might be reflective of an earlier C_{max} compared with that achieved by needle and syringe.

Despite this high-velocity and high-pressure delivery, once through the epidermal and dermal layers, the force with which the medication is being delivered is mostly spent. So, if another well-defined structure, such as a vein or artery wall is encountered, the delivered medication does not pass into that

structure but, rather, around it. As such, the J-Tip® can not be used to deliver medication intravenously or intra-arterially either deliberately or accidentally. Similarly, as the maximum penetration of agent is to 5–8 mm, the device is not designed to deliver intramuscularly. However, in a small child or an area where the subcutaneous space is very thin, some medication may pass into this compartment.

One potential problem using high-velocity and high-pressure delivery through a micro-orifice is that the medication, especially if of a high molecular weight, may be 'damaged' upon firing the device. In this study, however, the assessment of plasma anti-factor Xa levels demonstrated that the LMW heparin had indeed remained active following delivery by this device.

The J-Tip® is for single use and disposable thereafter. Being a needle-less syringe system, the risk of a health-care worker (or other individual) sustaining a needle-stick injury is eliminated and with it the potential for cross-contamination of blood liable to contain pathogens. Given increasing claims made against health agencies by individuals who have sustained needle-stick injuries, this aspect of the device becomes of a more fundamental importance. Already in California, USA, State legislature is such that soon only sheathed-needle systems or needle-less injection devices will be permitted for medication delivery, and the US Congress is debating whether to introduce this type of legislation USA-wide. Furthermore, agencies such as the World Health Organization who engage in mass vaccination programmes, often in areas of the world where HIV and hepatitis are rife, realise that the safest alternative delivery systems are indeed needle-less.

The potential applications and areas for needle-less systems to be used are many. In this study, we have delivered LMW heparin. Already, diagnostic agents have been delivered such as radioactive [^{99m}Tc]-labelled colloidal albumin for sentinel node detection in tracking the spread of a malignancy.[9]

A significant disadvantage in using needle-less injection systems such as the J-Tip®, however, is cost. It is estimated that, in low-volume usage, this device may cost up to £1.50–£2.00 per unit (compared with a few pence for a standard needle and syringe). In greater volume usage, this cost could perhaps fall substantially. However, as we have shown, patients do prefer needle-less delivery and the medication can be delivered satisfactorily. This, together with the additional safety implications, means that needle-less injection systems such as the J-Tip® are certain to be increasingly considered for use.

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