REVIEW ARTICLE

Hemophilia: Reducing Treatment Burden with Pen Devices

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Abstract

Hemophilia is a coagulation disorder caused by deficient or absent clotting factors. It is a chronic disease that starts from birth and requires lifelong intravenous administration of antihemophilic factors. Healthcare professionals (HCPs), patients living with hemophilia, and their caregivers have reported concerns regarding the challenges associated with the intravenous route and the deterioration in their quality of life (QoL) due to the frequently repeated infusions necessary to maintain the desired levels of clotting factors. Patients with hemophilia and their caregivers have often voiced their need for easier methods of treatment administration, similar to the way insulin is delivered subcutaneously using a pen. Subcutaneous injection using a pen device is a known way to improve treatment compliance and adherence in patients with chronic diseases. The recent introduction of pen devices for hemophilia treatment administration is expected to reduce the administration burden and improve QoL. The narrative review presents the advantages of pen devices and patient and caregiver attitudes toward these newly introduced pen devices in hemophilia.

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Introduction

Hemophilia is a rare inherited chronic disease (coagulation disorder) characterized by deficiency, reduced activity, or complete absence of clotting factors.[1–3] Hemophilia A (factor VIII deficiency) is more common than hemophilia B (factor IX deficiency), accounting for 80–85% of global hemophilia cases.[1,2] Hemophilia A is underdiagnosed in India.[2] According to a 2019 Indian Council of Medical Research report, there were approximately 80,000–1,00,000 cases of severe hemophilia in India, but only 19,000 cases had been registered with the Hemophilia Federation India.[4] Most patients in India (61.96%) present with hemophilia between 0 and 18 years.[5] Further, the majority (63.29%) had severe hemophilia, and another 22.78% had moderate hemophilia.[5]

Patients with hemophilia have an increased tendency for spontaneous and prolonged bleeding into joints, muscles, and other internal organs, thereby causing damage and pain.[1,6] In pediatric patients with hemophilia, these complications impact their education, play, and outdoor activities.[7] In adult patients with hemophilia, these complications restrict and compromise mobility, daily living, caring for children, and career options.[7] Thus, hemophilia significantly burdens patients, caregivers, and healthcare systems due to high morbidity and poor health-related quality of life (HRQoL), also demonstrated by the large HAEMOcare study conducted in developing nations, including India.[8]

Since deficient or absent clotting factors cause hemophilia, replenishing clotting factors is the absolute lifelong treatment for hemophilia.[1] The World Federation of Hemophilia (WFH) recommends prophylactic administration of antihemophilic factors as the standard of care for hemophilia.[1,2] However, in resource-limited countries like India, episodic (on-demand) clotting factor administration is a more practiced approach.[2,3,9]

Prophylactic treatment improves HRQoL and treatment costs by decreasing bleeding episodes, reducing hospitalizations and emergency department visits, reducing complications like joint damage and pain, and leading a more fulfilling life.[1,2] However, these treatment advantages are limited by the need for frequent and repeated parenteral administrations necessary to maintain the desired levels of clotting factors.[1,7,10,11]

A chronic disease like hemophilia, requiring repeated treatment administration and monitoring, possesses a massive treatment burden.[10] Therefore, a patient-centric approach in a chronic disease aims to relieve the treatment burden and help the affected individuals feel as disease-free as possible and not appear as "patients" to others.[12] Hence, the treatment paradigm of hemophilia is continuously innovating to reduce the treatment administration burden and improve the HRQoL of patients and caregivers. Introducing therapeutics that can be delivered subcutaneously with injector pen devices is a step toward reducing the administration burden.

Pen devices have been the preferred method for self-administering repeated subcutaneous injections of biologics in diabetes, rheumatology, and growth hormone deficiency.[13–16] The recent introduction of pen devices for hemophilia treatment administration is expected to reduce the administration burden and improve HRQoL. The narrative review presents the advantages of pen devices, and patient and caregiver attitudes toward these newly introduced pen devices in hemophilia.

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Hemophilia: Burden of Intravenous Administration

Hemophilia treatments are generally delivered intravenously. The intravenous route of administration has several drawbacks, as outlined in Box 1. Earlier, hemophilia treatments could only be administered in hospitals or clinics.[10] With access to better technology, home infusions have become a reality. However, home infusions are also cumbersome and time-consuming, need people with phlebotomy skills, have venous access issues, and can be painful.[10] Patients with hemophilia may permanently stop prophylactic treatment due to the burden of intravenous infusions.[10] Therefore, intravenous infusions impact treatment adherence and efficacy in hemophilia.[1,3,10,17–19]

Healthcare professionals (HCPs) treating patients with hemophilia identified several treatment administration burden issues in their patients, such as the ability to insert the needle correctly, find good venous access, carry out the infusion steps, and prepare and administer the treatment.[10] The HCPs felt that infusions had an emotional impact on patients because they feared they would lose the venous access or that it might become infected, and they also questioned their ability to self-infuse. For patients who did not have good venous access, there was an additional burden of getting a port or a peripherally inserted central line.[10] These burdens were further enhanced due to the need for repeated and frequent infusions.[10]

People with hemophilia and their caregivers have repeatedly expressed that they experience several challenges (economic, physical, educational, and technical) with these intravenous treatments that impact their QoL.[7,10,20] The patients with hemophilia identified several challenges with the infusion treatments, including packaging, storage/refrigeration of medications, and reconstitution.[7,10] Traveling for treatment, treatment time, treatment schedules and frequency, interference with daily life, pain, skin scarring, and emotional trauma were other concerns of patients with hemophilia and their caregivers.[7,10,11]

People with hemophilia and their caregivers voiced the need for treatments with longer-lasting effects and treatments that could be delivered through an alternative or easier method.[7,20]

Box 1: Drawbacks of intravenous factor concentrates[1,3,10,17–20]

- Coordination of treatment schedules with hospital/clinic staff
- Complicated home infusion scenarios
- Skilled or trained individual's availability for frequent intravenous infusions
- Challenges with venous access
- Considerable time commitment
- Portability
- Injection pain
- Poor treatment adherence
- Reduced quality of life (QoL)
- Emotional impact & fear of stigma

Exploring the Subcutaneous Route for Hemophilia Treatment

Self-management is an important strategy in any chronic disease, known to improve patient HRQoL and adherence to treatment. For patients with chronic diseases such as hemophilia and diabetes that require parenteral treatment administration, self-reliance and compliance can be achieved by improving convenience and ease of treatment administration.

Administering parenteral drugs through a subcutaneous route is a strategy toward self-reliance for treatment administration. The subcutaneous route of administration has been successfully deployed to deliver other biologics (e.g., insulin and growth hormone) and has several benefits over the intravenous route.[2,3,17,19] The subcutaneous route allows self-administration with a much smaller needle size, reduces treatment burden and injection pain, and improves convenience and treatment adherence.[2,3,17,19]

This has been amply demonstrated in diabetes, where patients on insulin therapy self-administer insulin subcutaneously. Many patients with type 2 diabetes (T2D) mellitus also face an insulin injection burden during the T2D disease trajectory due to progressive beta-cell failure.[21] Insulin injection is the only way to replenish complete insulin deficiency for patients with type 1 diabetes (T1D) mellitus.[21,22] Since T1D starts in childhood, just like hemophilia, the treatment administration burden starts early in the life of the patient with T1D and the caregiver.[22]

A recent survey conducted in the US and the UK showed that patients with hemophilia and their caregivers significantly preferred the subcutaneous route over intravenous administration.[23] The challenges with administering hemophilia treatment through the intravenous route were overcome by developing nonfactor products, such as emicizumab and anti tissue factor pathway inhibitors (anti-TFPI), that could be administered through a subcutaneous route.[2,3,17,19,24]

Subcutaneous Administration through Injector Pen Devices

Despite the advantages of subcutaneous drug administration over the intravenous route, traditional ways of injecting medication subcutaneously require vials and syringes. However, patients and caregivers face many challenges while using vials and syringes, such as a cumbersome and time-consuming process (Box 2).[17,21] This impacts treatment adherence, psychosocial well-being, and overall HRQoL.[17]

Ready-to-use prefilled syringes (PFS), auto injectors, and other pen devices overcame the disadvantages of syringes and vials.[26] These devices conferred many advantages for patients and their caregivers, including dose accuracy, improved HRQoL, and others, as shown in Box 3.[1,17,26]

The journey of ready-to-use devices began with the introduction of PFS in the subcutaneous administration landscape.[26] However, PFS use was limited by many manufacturing and other challenges, including compatibility between the drug formulation and the material of the syringe and the rubber stopper; the inability to maintain drug functionality throughout its

Box 2: Disadvantages of administering subcutaneous injections with vials and syringes[17,21,25]

- Cumbersome packaging and storage
- Need for reconstitution
- Possibility of contamination during reconstitution
- Drawing erroneous dosing
- Medication wastage
- Time-consuming as several steps are required for preparing the injection

Box 3: Advantages of pen devices over traditional subcutaneous administration using vials and syringes[1,16,17,21,23,25–28]

- Ready-to-use injection device
- Dose accuracy and better therapeutic efficacy
- Less medication wastage
- Long-term cost-effectiveness
- More flexibility
- More discreet and easily portable
- Quicker to use
- Ease of use and easier administration
- Better patient acceptability and compliance
- Fewer resources (single pen over vials and syringes)
- Reduce needle phobia and injection anxiety
- More socially acceptable

shelf life; and the incompatibility between the formulation's viscosity and the requisite syringe-needle configuration, etc.[26] Further, patients need to manage the force with which they inject the formulation.[26]

Since the introduction of the insulin pen in 1985, using pen devices has been an acceptable practice for subcutaneous self-administration.[12,21] The continuous innovation of pens using a patient-centric approach has revolutionized the HRQoL of patients with chronic diseases and their caregivers.[12,21] These innovations prevented medication wastage by introducing features such as dose dialing and allowing half-unit dose increments.[21] Features such as touch buttons, color-coded cartridge holders, dose magnification windows, audible click with each unit dialed, and prominent dose arrows and labels improved convenience and ease of use for patients of all age-groups.[21,27] Pens were adapted for pediatric patients by creating colorful, discreet designs, memory function, and the ability to inject with reduced force.[21,29] The advent of connected pens and "smart pens" further eased dose calculations, dialing, reminders, and monitoring.[21]

Further patient-reported outcomes show that patients feel more confident in their ability to self-administer the drug with pens, as they find pens "more stable" and "easier to handle" than syringes.[27] Patients perceived pen devices as more socially acceptable and felt that pens allowed better disease (diabetes) self-management than vials and syringes.[27]

Advantages of Pen Devices in Hemophilia: Clinical Evidence

A patient experience study showed that several patients with hemophilia desired a mode of administration similar to an insulin pen.[7]

A recent US and UK survey reported that patients with hemophilia preferred a prefilled pen over vials and syringes.[23] Another recent large utility study conducted in the UK, Canada, and the US showed that people living with hemophilia in these countries assigned a lot of importance to the injection device.[1] Patients with hemophilia and their caregivers reported a significant utility gain with monthly subcutaneous injections with a prefilled pen device vs subcutaneous injections with a syringe and IV infusions.[1] Using less time-consuming and easy-to-use pen devices was expected to improve HRQoL significantly.[1]

Using pen injection devices in hemophilia is a breakthrough that is likely to revolutionize the treatment landscape. No pen devices are available for subcutaneous administration of non factor products like emicizumab. However, pens and microneedle devices have been recommended for precise dosing and reducing drug wastage of emicizumab.[25] Precise dosing is necessary for therapeutic efficacy. Currently, concizumab pen injector are available only for subcutaneous anti-TFPI administration.

Concizumab Pen Device in Hemophilia A or B

Concizumab is a once-daily novel anti-TFPI monoclonal antibody that can be subcutaneously delivered once daily using a prefilled, multidose pen-injector for prophylactic prevention or reduction of bleeding episodes in patients with hemophilia A or B with or without inhibitors.[17,30] Analysis of landmark trials (Explorer 4,[31] Explorer 5,[31] Explorer 7,[32,33] and Explorer 8[34]) demonstrates that subcutaneous concizumab prophylaxis improves HRQoL and reduces treatment burden. The injection is approved in hemophilia A or B patients with inhibitors and shows similar benefits in the ongoing Explorer 8 study in hemophilia A or B patients without inhibitors.[30,33]

The concizumab pen-injector has an easy-to-use mechanism to set the precise dose and is an adapted version of the FlexTouch insulin pen, which demonstrates dosing accuracy (ISO 11608–1 certified) across a wide dose range (10–400–800 µL).[17,30,35] The pen-injector has disposable, single-use small (4 mm long) and thin [32 gauge (G): 0.23/0.25 mm] needles.[17,30] The 4 mm pen needle is the shortest and requires low thumb force, making it more comfortable and easier to use.[21] Pens with 4 mm and 32G needles are the gold standard.[36] They reduce needle pain, restrict the needle to subcutaneous space only, prevent injection from entering muscles, and are also suitable for pediatric patients and those with needle phobia.[21,27,36] Smaller needle size facilitates almost painless drug delivery in everyday life settings.[37]

Patients have reported ease of use, precise dosing, and satisfaction with the concizumab pen-injector. A recent study demonstrated that 98% of the patients using emicizumab or any other factor replacement therapy could independently administer concizumab at their first attempt with an average injection time of 1 minute 21 seconds.[17] In this study, the adult patients had been on treatment for an average of 25 years, and patients cared by caregivers and adolescents had been on treatment for an average of 12 years. The pen-injector was assessed as "easy" or "very easy" to learn and use by 97% of adults and 96% of adolescent participants; 99% found the pen-injector easy to prepare for use; 98% found it "easy" or "very easy to use"; 88% of participants on factor replacement therapies and 82% of participants on emicizumab preferred the concizumab pen injector over their current injection method.[17]

Further, 95% of the participants reported that the pen-injector was easily portable and could be used outside the home; 97% were "very confident" or "extremely confident" that they could correctly use the pen-injector; 84% were "fully confident" that the correct dose was delivered, and 12.5% were "somewhat confident." All the adults and caregivers reported that medication preparation and injection time with the pen-injector was "quick" or "very quick."[17]

Marstacimab Pen Device in Hemophilia A or B

Marstacimab-hncq is a prophylactic anti-TFPI administered subcutaneously with a single-dose prefilled syringe or single-dose auto-injector pen once weekly to prevent or reduce bleeding episodes in adults and adolescents with hemophilia A or B without inhibitors.[38] The phase 3 BASIS study (NCT03938792) demonstrated a significant decrease in annual bleeding rates (ABRs) with marstacimab subcutaneous injection compared to routine prophylaxis with factor products ($p = 0.0376$), and the results were consistent across all hemophilia types and age subgroups.[39] The improvement in HRQoL with marstacimab was non inferior to that achieved *via* routine prophylaxis.[39]

Early results from an ongoing study reported a delivery system success rate of 99.2% by patients and caregivers who administered weekly marstacimab flat-dose using a prefilled auto-injector pen for ≤6 consecutive weeks.[29] Participants had completed the phase 3 BASIS study and had either severe hemophilia A (factor VIII <1%) or moderate to severe hemophilia B (factor IX ≤2%) with or without inhibitors. All the participants could inject the full marstacimab dose with the auto-injector prefilled pen, except one participant at week 2, and all participants reported ease of use.[29] No pen-related adverse event was reported by any patient or caregiver except one incorrect dosing.[30–39]

Future Insights

There is an unmet need to reduce the treatment administration burden in hemophilia. Targeting the subcutaneous route and developing pen devices are expected to reduce the treatment administration burden. The experience with pen devices in hemophilia can be further enhanced by improving injection rates,

customizing injection speed and duration, and developing connected devices to provide injection logs and reminders or real-time stepwise instructions.[16,40]

However, the designs and features of future pen devices in hemophilia should address the requirements and expectations of the end users (patients and caregivers) of all educational and age backgrounds.[12,41] Well-designed questionnaires, surveys, and product prototype testing should be conducted with end users.[12,27,41] Improved patient-centric hemophilia pen devices will likely improve treatment adherence, therapeutic efficacy, and HRQoL.

Conclusion

The subcutaneous route and pen devices are slowly revolutionizing the treatment administration landscape in hemophilia. The review highlights early results demonstrating patient and caregiver acceptance, preference, ease of use, and satisfaction with pen devices over traditional subcutaneous or intravenous hemophilia treatment administration methods.

Ethics Compliance

This is a narrative review and hence does not require EC approval.

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All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

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