Intramarrow injection needle: a new technique to treat patients with haematological and non-haematological malignancies by directly injecting therapeutic agents into the bone marrow cavity

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ABSTRACT

Aims The purpose of this report is to describe a new instrument designed for the injection of therapeutic agents directly into the bone marrow cavity as well as to aspirate bone marrow specimens for the diagnostic purposes.

Methods The instrument consists of three parts: the needle, stilette and an adjustable guard. The overall length of the needle is 76 mm and has uniform external diameter except for the distal penetrating segment, which is sharp but short and safe to use on the sternum. The proximal end of the needle is fitted with a plastic T-bar handle, which is ergonomically designed for firm grip and easy manoeuvrability.

Results The instrument has been designed to obtain bone marrow aspirate specimens as well as to inject therapeutic agents into the posterior ilium.

Conclusions The rationale for the intramedullary injection of therapeutic agents for the treatment of patients with leukaemia, lymphoma and other haematological and non-haematological malignant disorders is described. In an emergency when intravenous therapy becomes difficult due to collapsed veins, this instrument may be used for direct intramarrow infusion of blood and blood products.

INTRODUCTION

Intravenous administration of chemotherapeutic agents remains the primary modality of treatment for patients with leukaemia, lymphoma, multiple myeloma and other haematological malignancies. Cytosine arabinoside, daunorubicin, vincristine, rituxan, fludarabine, mitoxantrone, bortezomib and other antineoplastic drugs are all administered intravenously. However, intravenous chemotherapy does have limitations. One is that the drugs are diluted many fold as they enter into circulation and mix with approximately 5 L of circulating blood. And as a result when they reach their target organ, particularly the bone marrow, their effective concentration becomes much less than when they were injected into the vein. In addition, during their journey/circulation, they may also bind specifically or non-specifically to proteins or other tissue components and become less effective or ineffective. At some point the drugs may also be subjected to alteration and deactivation by the liver and other organs before the agents reach their target organ. There are, however, limitations of this technique such as inadvertent injury to great blood vessels and the heart during sternal injection. It is also not possible to know the origin of the disease in the bone marrow and like the intravenous administration of therapy the drugs potentially bind to plasma proteins and may be adversely affected when they pass through the liver.

The technique of intramarrow injection delivers the active agent(s) directly into the bone marrow, the originating site of the leukaemic or other haematological malignant process.[1] Admittedly an injection into a reservoir of haematopoietic marrow in the posterior ilium or the sternum may not directly affect other bone marrow sites, but agents released here will be absorbed by venous sinusoids of this highly vascularised organ and will ultimately reach distal bone marrow regions almost as effectively as by conventional (intravenous) methods of administration. Thus, the overall effect achieved by intramarrow therapeusis is a more intimate association of the chemotherapeutic drug(s) with a large number of target cells and at a high concentration, with potential enhancement of antineoplastic activity, as well as the effects attained by the conventional intravenous approach. Furthermore, the direct intramarrow injection of cytotoxic or anticancer agents may not only eliminate a significant proportion of the rapidly dividing malignant cells but may also affect the regulatory stromal cells that control haematopoiesis and help bring about a favourable outcome by immunomodulation and the elaboration of hitherto unknown, but clinically useful extracellular factors like cytokines.

MATERIALS AND METHODS

Instrument

The needle (figures 1 and 2) consists of three parts. The needle (A) has an overall length of 3 inches (76 mm), a uniform external diameter of 2.00 mm except for the distal 2 mm portion where it is bevelled to be in line with the stilette. The distal penetrating segment of the needle has a short bevel made at an acute angle and trimmed at the sides to produce a trocar-pointed end (figure 1 upper inset) for easy penetration of the skin, soft tissue and bone over posterior ilium and anterior plate of the sternum. Unlike the conventional aspiration needles where the tips of the needles are too long, the penetrating end of this needle has been deliberately made short to avoid impaction and accidental

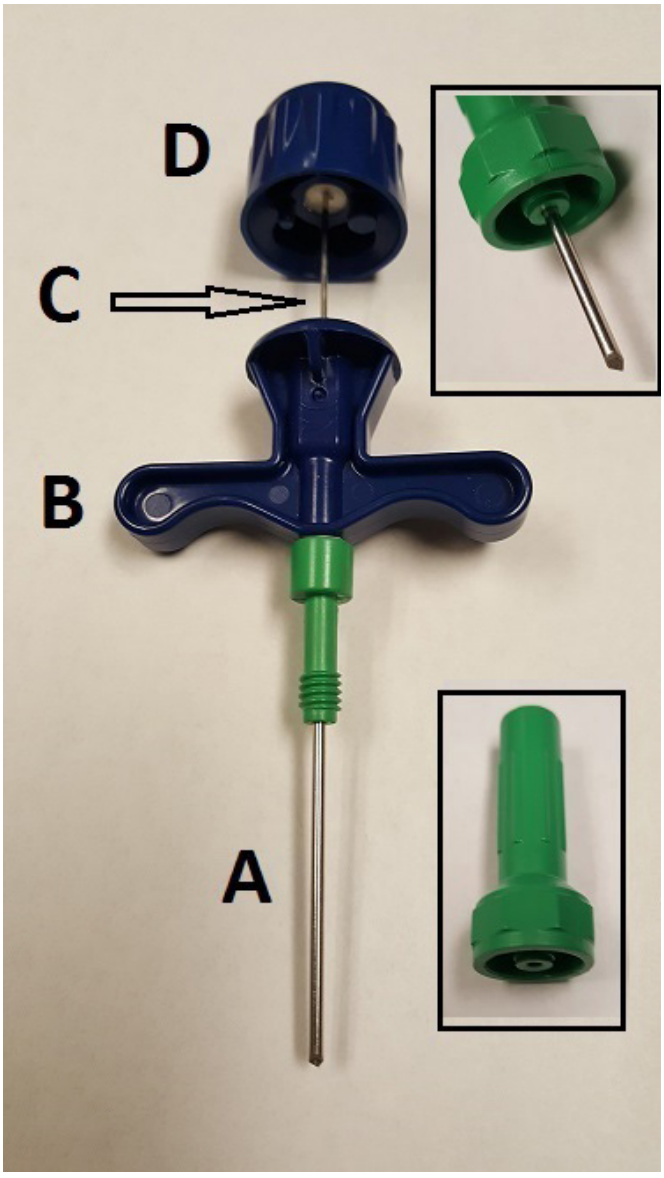

Figure 1 shows the needle (A), T-bar handle (B), the stilette (C) and the handle of the stilette (D). The upper inset shows the tip of the needle in greater detail. The lower inset shows the adjustable guard.

Figure 2 shows the complete needle assembly with the adjustable guard in place.

penetration of the posterior plate of the sternum. As a result the needle is much safer to use in this location.

The proximal end of the needle is fitted with a prominent plastic T-bar handle (B), which is ergonomically designed for easy manual fitting and firm grip. The top of the T-bar handle is round and slightly convex to receive the bottom concave part of the handle of the stilette (C). The top of the central area of the T-bar handle has an aperture to receive the nozzle of a syringe to complete the bone marrow aspiration or bone marrow injection procedure.

The stilette (C) is a solid stainless steel shaft of 1.8 mm in diameter. Its tip is bevelled to be in line with the inner wall of the needle (figure 1 upper inset). The proximal end of the stilette is fitted with a solid plastic handle (D) which is 20 mm long and 30 mm wide in diameter. Its proximal (top) portion is smooth and convex. The distal (bottom) area is concave to fit on to the convex plastic dome of the T-bar handle.

The adjustable guard (lower inset) which is used to control the depth of penetration during the sternal puncture procedure. While using this needle for iliac bone marrow aspiration or direct iliac intramedullary injection, this guard is removed before use.

This instrument has also been designed to obtain bone marrow samples from the sternum and ilium as well as injection of medication or chemotherapeutic agents directly into these marrow cavities. This needle can also be used for infusion of fluids, blood and blood products into tibias or other readily accessible bone marrow sites particularly when veins are difficult to find or are collapsed.

The space between the anterior and posterior plate of the sternum is shallow (figure 3) and if the penetrating end of the needle is too long then there may be a possibility of penetrating the posterior plate of the sternum and thus injuring the sub adjacent great blood vessels. Considering this in mind, the penetrating end of the needle has been designed to be short (figure 1 upper inset) but it has been sharpened at its side as to make it trocar pointed so that it can easily penetrate the skin, soft tissue and the sternal and iliac bone.

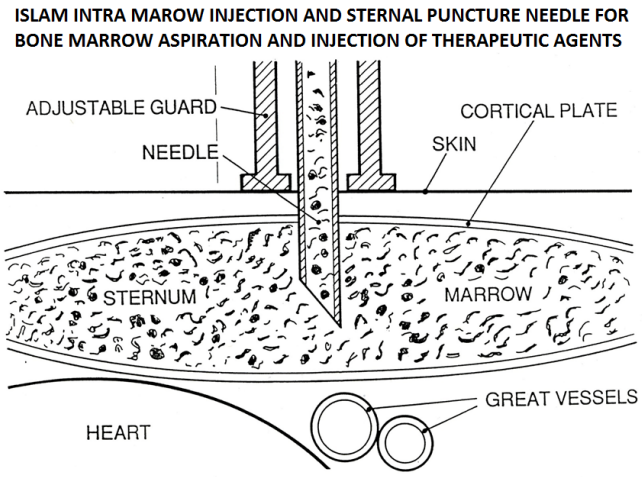

Figure 3 Schematic representation of the Islam sternal puncture procedure with respect to posterior plate of the sternum and the great blood vessels that lie underneath.

Injection/aspiration procedure

Sternum

The patient is placed in a level supine position with his/her head and neck comfortably resting on a soft low-lying pillow. In men, it may be necessary to shave the skin over the sternum prior to aspiration or injection procedure. The injection and aspiration procedure is performed at the proximal region of the body of the sternum, at the level of the second intercostal space, half away between the midsternal line and the left or right sternal order. The area is identified by palpation and the location is marked with indelible marker or digital pressure. The area is surgically prepared down to the fourth intercostal space with alcohol and iodine and the site is draped. Following the routinely accepted precautions of skin sterilisation and local anaesthesia of the skin, subcutaneous tissue and periosteum, the bone marrow needle is slowly advanced through the skin and subadjacent tissue in a perpendicular direction to come in contact with the anterior plate of the sternum (figure 4). When it is reached, the cortical bone is then penetrated by gentle rotary motion of the needle by griping the T-bar handle. Once the cortex is penetrated, the needle is slowly advanced into the marrow cavity with gentle clockwise-counter-clockwise rotary motions until an adequate depth (only a few millimetres) is reached. Once the needle is in place in the marrow cavity, the trocar is withdrawn and the intramarrow injection or bone marrow aspiration is performed.

Ilium

The instrument is also designed to obtain bone marrow aspirate specimens as well as to inject therapeutic agents into the posterior ilium. The techniques of aspirations from these sites have been previously described.[2] The patient is placed in a right or left lateral decubitus position with the top knee bent forward and drawn up and the back comfortably flexed or in the prone position with a pillow beneath the hips. The site of posterior iliac crest is identified by palpation and with the use of sterile technique, the overlying skin is prepared with antiseptic and draped. Then the skin, subcutaneous tissue and the periosteum are infiltrated with a local anaesthetic. A small 3 mm skin incision may be made with a sharp pointed scalpel blade. The needle with the stillette in place but without the guard is advanced slowly through the incision, pointing towards the anterior superior iliac spine (figure 5) and when the posterior ilium is reached it is then penetrated by gentle rotary motions of the needle. Once the needle is in the marrow cavity, the stilette is then withdrawn, a syringe is attached and the injection/aspiration procedure performed.

Figure 4 Demonstrate the method of injection of therapeutic agents directly into the sternal marrow cavity.

RESULTS

The needle as a portal of injection has been extensively tested on unembalmed human cadavers using a small (3–5 mL) amount of normal saline and methylene blue. The needle remained tightly stabilised within the confines of bone and marrow and no spillage of saline or methylene blue was observed during the injection procedure. The construction and handling of the needle have been found to be satisfactory.

DISCUSSION

The bone marrow is a haematopoietic organ, which is primarily affected in leukaemias, lymphomas, multiple myelomas as well as some other haematological and non-haematological malignant conditions. The intravenous administration of chemotherapeutic agents is accepted as the norm in most cancer centres throughout the world. However, direct injection of medicinal agents into the marrow cavity may have advantages. In a bone, such as the ilium or sternum, the employment of this mode of treatment directly exposes a considerable volume of diseased marrow (leukaemia/cancer cells) to the drug at a high concentration. In addition, a

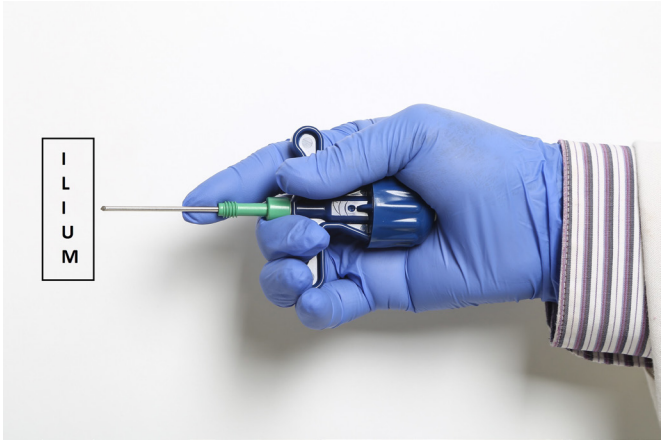

Figure 5 Demonstrate the method of injection of therapeutic agents directly into the iliac marrow cavity.

large proportion of the drug(s) would also be absorbed from the injected sites and enter into the blood stream and able to circulate systemically reaching/affecting the target cells in other parts of the body. As a result, the overall therapeutic effect might even be better than that achieved by intravenous therapy alone.

The introduction of antineoplastic agents directly into the marrow cavity and at a concentration higher than that achieved by the intravenous route could bring about a rapid destruction of a significant proportion of the proliferating malignant cell population. Such destruction of malignant cells could well also bring about the process of necrosis and thereby attract macrophages and other accessory cells to the site of cell destruction. The overall and combined effect of the interaction of the administered drug and the altered microenvironment (stromal, macrophages, necrotic cells) may be viewed as having the potential to support an enhanced antineoplastic outcome.

Apoptosis and bone marrow necrosis have been known to be associated with a spontaneous remission of some malignant diseases.[3 4] Although the mechanism of such remissions remains unknown, it is thought to be the result of an efficient immune response against malignant cells. A related effect may be observed in the spontaneous remission of virus infections such as varicella or the effect of vaccinations like smallpox, which are known to be mediated by endogenous interferon production.[5 6]

It is known that the effectiveness of an antineoplastic agent varies considerably depending on the route of its administration.[7 8] It is also recognised that the success of a therapeutic agent is dependent on its ability to localise in malignant tissues in optimal quantities.[9] In that context the advantage of direct intramarrow injection of chemotherapeutic agents is quite obvious. The benefit of this present method resides in its simplicity, and in the fact that antineoplastic drugs can be given directly and at a higher concentration into the bone marrow cavity. A chemotherapeutic agent, once injected into the bloodstream of a patient, encounters the following physiological barriers before it reaches the target cancer cells: (1) distribution through the vascular space; (2) movement across the microvascular wall; (3) transport through the interstitial space among cells and (4) transport across the cell membrane.[9] During each of these transport processes, a drug molecule may be metabolised and undergo degradation or bind specifically or non-specifically to protein or other components thus becoming less effective or ineffective. The present technique of direct intramarrow injection of chemotherapeutic agents has the potential advantage of overcoming most if not all of the above physiologic barriers that a bloodborne molecule (drugs) has to encounter before it reaches its target (cancer) cells and hence making the treatment more effective.

The sternum and ilium are closed marrow cavities. Thus, when drugs are injected into these marrow cavities, they rapidly disperse throughout these organs by perfusion and capillary action. In addition, drugs are also absorbed via the rich sinusoids of these marrow cavities and enter into circulation and thereby reach all other parts of the haematopoietic marrow.

This new approach may prove to be very useful in the present environment of cost cutting and managed care. Should intramarrow injection therapy prove to be effective (as has been the case in our two such treated patients)[10 11] then many of the leukaemic patients may be effectively treated on an outpatient basis. This would be a major improvement from the patient's point of view whose hospitalisation will be either completely avoided or kept to a minimum, thereby improving one's quality of life.

Like most treatment modalities, the adverse effects of intramarrow injections of therapeutic agents may include fever, myalgia, bone pain, malaise and rash. It is believed that serious side effect such as tumour lysis syndrome is highly unlikely because of the smaller dose that is used (eg, 30 mg/m^2 body surface instead 100 mg/m^2 of cytosine arabinoside).

Take home messages

- The bone marrow is a haematopoietic organ, which is primarily affected in leukaemias, lymphomas, multiple myelomas as well as some other haematological and non-haematological malignant conditions.
- The intravenous administration of chemotherapeutic agents is accepted as the norm in most cancer centres throughout the world.
- Injection of medicinal agents directly into the marrow cavity may have advantages. In a bone, such as the ilium or sternum, the employment of this mode of treatment directly exposes a considerable volume of diseased marrow (leukaemia/cancer cells) to the drug and at a high concentration.
- In addition, a proportion of the drug(s) would also be absorbed from the injected sites and would therefore enter into the blood stream and be able to circulate systemically reaching/affecting the target cells in other parts of the body.
- As a result, the overall therapeutic effect might even be better than that achieved by intravenous therapy alone and with little or no side effects and improved patient tolerability.

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