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Maximizing Intra-Articular Therapy for Osteoarthritis and other Joint Diseases: Continuous Infusion Device for Prolonged Drug-Target Residence Time

Sergio Crimaldi[1*], Paolo Mario Sarais[2], Antonio Devito[3], Alberto Migliore[2,4]

Abstract

Intra-articular injections in the management of Osteoarthritis, offer notable advantages such as enhanced bioavailability. However, despite resorting to intra-articular injection as a direct method for local administration, free drugs often struggle to linger within the joint space for sufficient periods. This struggle compromises the achievement of their biological objectives at a consistently satisfactory level and duration. Since the main determinant for intra-articular drug administration in osteoarthritic joints is pharmacokinetics, we propose a new medical device to maintain a constant level of product inside the joint. This is an infusion pump with permanent catheter into the joint, specifically designed for intra-articular infusion and capable of administering articular products continuously over time. The potential advantages of this pump can be: prolongation of residence time of therapeutics (ranging from a few hours to several days); ensuring the correct dose; avoiding the use of crystals for "depo" effect; instantaneous modulation of administration speed; transportability and wearability, eliminating the need for hospitalization. However further studies are needed to confirm the safety of the use of this articular pump infusion and to determine correct indications, appropriate products and proper volume and dosage to administer in each clinical case.

Keywords: Osteoarthritis; Intra-articular drug administration; Intra-articular Residence Time; Continuous articular infusion device; Hyaluronic acid; Joint infusion pump

Background

Osteoarthritis (OA), a condition impacting over 19% of the U.S. population aged 45 and above, presents a significant challenge. It leads to the gradual deterioration of joint tissues, resulting in pain and decreased mobility. Despite extensive research, there is still no medication capable of delaying the disease's progression by slowing down cartilage degeneration or promoting tissue regeneration. Presently, available treatments focus solely on alleviating pain after symptoms manifest. Various products and administration routes, including local and systemic approaches, exist. Local administration, particularly through intra-articular injection, offers notable advantages such as enhanced bioavailability, reduced systemic interaction, fewer off-target effects, potential mitigation of systemic adverse events, and often lower overall medical costs.

Many diarthrodial joints, especially those affected by OA, lend themselves well to local drug administration. OA, impacting individual joints, and

Affiliation:

[1]Humanitas Research Hospital, Milan, Italy

[2]Associazione Nazionale per la Terapia Intra articolare dell'Anca con Guida Ecografica (ANTIAGE), Rome, Italy

[3]Orthogeriatric Service, Ospedale San Pietro Fatebenefratelli, Rome, Italy

[4]U.O.S. of Rheumatology, Ospedale San Pietro Fatebenefratelli, Rome, Italy

***Corresponding Author:**
Sergio Crimaldi, Humanitas Research Hospital, Milan, Italy.

Email: sergiocrimaldi@gmail.com

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inflammatory conditions like rheumatoid arthritis (RA) and gout, affecting multiple joints, pose a high incidence and prolonged therapeutic demand. Current systemic treatment options often fall short for patients, fueling a growing interest in achieving optimal therapy localization at the pathological site. This approach aims to maximize effectiveness while minimizing systemic adverse events, reflecting the current emphasis on improving patient outcomes [1].

The clinical challenge in treating osteoarthritis lies in the inadequate local administration of drugs to joint tissues. Despite resorting to intra-articular injection as a direct method for local administration, free drugs often struggle to linger within the joint space for sufficient periods. This struggle compromises the achievement of their biological objectives at a consistently satisfactory level.

The main determinant for intra-articular drug administration in osteoarthritic joints is pharmacokinetics. Once injected into the joint capsule, the drug navigates through the synovial fluid, undergoing rapid physiological turnover. Consequently, the drug is swiftly drained and lost in the systemic circulation through the venules and lymphatic vessels of the synovial membrane.

Free drugs face elimination from the joints within a short timeframe, typically a few hours or days. Given this limited duration of effectiveness, physicians often seek to minimize the frequency of intra-articular injections. The interval between injections varies based on the doctor's judgment and the specific drug used, commonly falling within the range of 2-12 weeks. Consequently, the ineffectiveness of many osteoarthritis treatments is not surprising.

The therapeutic challenge intensifies when targeting the articular cartilage, a common focus in osteoarthritis treatment. This tissue, lacking blood vessels, permits drug penetration solely through diffusion. However, this diffusion encounters obstacles within the dense, highly anionic extracellular matrix of cartilage. The small pore size (less than 15 nm) hinders efficient diffusion, and the process is slower than the joint clearance rate. Consequently, free drugs within the joint space are often eliminated before reaching therapeutic concentrations deep within the cartilage, limiting their efficacy [2].

Understanding the kinetics of drug binding and unbinding provides insights into drug efficacy. Specifically, residence time proves more effective than conventional thermodynamic parameters in predicting in vivo efficacy. While measuring the on-rate and off-rate of a drug was initially challenging and expensive until the early 2000s, subsequent advancements addressed these limitations [3,4].

Two crucial parameters in this context are residence time (RT) and mean residence time (MRT). RT signifies the duration a drug remains in contact with its biological target, while MRT represents the average total time a drug molecule spends in the introduced kinetic space. It is influenced by the drug's administration method and elimination factors. In the one-compartment model following intravenous administration, the MRT is consistently greater than the half-life (t1/2) of a drug. The half-life (HL) denotes the time required to eliminate 50% of the drug from the body. Typically, and simplifying, the residence time is longer than the half-life by a factor of 0.37. This principle is applicable to the articular space as well [5].

The challenge of prolonging binding due to an extended drug-target residence time hinges on the slower dissociation of binding compared to drug elimination, highlighting a weakness in the system. When applying these principles to the articular space, measuring in vivo becomes intricate due to numerous variables influencing product clearance. The literature on articular residence time is sparse, particularly regarding in vivo studies.

Regarding Hyaluronic Acid (HA), Balazs noted limitations in its clinical indications due to the physical properties and short residence time of the natural HA molecule. He proposed enhancing these parameters through chemical modifications like cross-linking processes [6]. Various types of HA products exhibit variable half-lives (HL), such as unmodified HA (HL < 1 day), Hylan GF20 A (HL 1.5 days) or B (HL 6.8 days), and strongly modified HA (HL > 20 days, often used in rabbit or goat models) [7-9]. Abatangelo further confirms the potential to prolong the effect of HA in the articular joint using numerous derivatives to reduce the need for repeated intra-articular injections [10].

However, the mechanism of action for HA products remains an open question. Whether efficacy is exerted through binding to receptors, mechanical/rheological properties, or a combination of both raises complexities. Calculating the rate corresponding to each mechanism remains a challenge.

In contrast, corticosteroids and other products (e.g., albumin, lidocaine, anakinra, lubricin, and NSAIDs) for articular administration exhibit a short mean residence time (MRT) ranging from hours to days. The clearance rate often proves insufficient to optimize their clinical effect. Precisely calculating articular clearance in vivo remains elusive. Despite similarities in clearance patterns among products, variable drug efficacy linked to clearance emphasizes the need to consider articular clearance as a conceptual rather than a precise measure.

Several variables influence articular clearance, including genetic and anatomical variability affecting diffusion through synovia, blood and lymphatic clearance, presence of lytic enzymes, individual innate immune system differences, product variables like form, size, and polarity, pathological

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factors such as inflammation and degenerative pathologies, and the presence of co-morbidities and obesity [11].

Hypothesis

How can we address articular clearance more effectively? Various approaches have been proposed and investigated. Altering the volume or concentration of products, such as using larger molecules, can increase clearance from within but decrease clearance through the synovial membrane and vessels [12]. Conversely, smaller molecules yield the opposite effect. Another strategy involves incorporating carriers like nanomaterials, microspheres, drug delivery systems, or matrices, although these often end up remaining in the intercellular space or inside cells like "rubbish." The association with other drugs to limit clearance or inflammation is a lengthy and costly approach [13-17].

Another potential solution lies in hydrogel composition. However, Gupta highlights that despite the potential benefits, data on preclinical safety and efficacy studies are lacking. Rigorous studies are needed to establish a useful correlation between research findings and clinical safety and toxicity studies. Further efforts should focus on improving hydrogel design for combination therapy, controlled drug release, overcoming long-term treatment challenges, and reducing treatment costs [18].

While these approaches may enhance the clearance curve, can we explore a different route? Consider driving or administering therapeutic substances in a novel way. The current techniques, limited in their pattern of administration, result in an up-and-down concentration curve of the injected product. We could attempt to transform the clearance curve into a steady-state curve, maintaining a constant level of product within the joint environment. This could be achieved through a new medical device designed to administer articular products continuously over time. In other medical contexts, infusion pumps with permanent catheterisms have been used for antalgic therapy (epidural), insulin therapy (subcutaneous), or chemotherapy (endovenous). Surprisingly, there is currently no available device specifically designed for joint infusion.

Introducing a new Class IIb continuous articular infusion device, miniaturized and wearable, could be a game-changer. Recently patented, this device comprises two parts: an electromechanical part programmable on-board or with a dedicated app for mechanical propulsion and a sterile consumable part with a tank (providing perforated access) and an infusion set with a catheter. The catheter, insertable through an 18G needle and fixable with a common steril medication, eliminates the need for a surgery room. Placement in a no-load space, like the over patella space of the knee, along with a Velcro band and a bag, ensures the pump remains secured to the patient during infusion.

Evaluation of hypothesis

The potential advantages of this device are extensive:

- Prolonged therapies for days (ranging from a few hours to several days)
- Ensuring the correct dose
- Prolonging the articular resident time of drugs
- Avoiding the use of crystals for "depo" drugs
- Allowing instantaneous modulation of administration speed (slower or faster at a given moment)
- Being transportable and wearable, facilitating its use for Home Care and eliminating the need for a hospitalization device

The primary disadvantage could be infection, likely comparable to other catheterism procedures. Dawson's literature review [19] found rates of deep infection ranging from 0% to 0.7% and rates of superficial infection ranging from 1.8% to 12% in permanent percutaneous epidural catheterism procedures. Nevertheless, the same device can be repurposed to administer intra-articular antibiotics. Other minor issues may be related to incorrect use or malfunctioning, surpassing the security systems of the device.

This device, designed exclusively for medical use, holds promise for various intra-articular drugs, joints, and articular pathologies. Some potential applications include addressing therapy failures, recovering low molecular weight hyaluronic acid and short-half-life products commercially, improving post-surgery rehabilitation in cases of pain, modulating drug infusions in research laboratories, and administering appropriate antibiotic dosages for septic arthritis, including cases involving prostheses. The device may help address two unmet needs in infiltrative therapy: ensuring good drugs are given optimally for increased effectiveness and providing a simpler, minimally invasive solution to the complex problem of local intra-articular treatment.

Empirical data

Preliminary clinical and technical tests have been conducted on a restricted number of patients as part of a series of personal observations. As an example, we report the case of a 74-year-old woman, 160 cm tall and 73 kg, affected by knee osteoarthritis of grade 3 according to Kellgren Lawrence radiological degree [20]. She underwent conventional non-surgical treatments during the initial three years after diagnosis. In particular, during the last two years (2021-2022), she received six injections of hyaluronic acid—respectively three with high molecular weight (HMW), and two with cross-linked HA products, and one with corticosteroid. In the course of this period, she underwent three arthrocenteses, with the extraction of 20 ml of intra-

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articular fluid (citrine) each time. In June 2021, our device has been implanted for continuous intra-articular infusion in the symptomatic knee. A solution containing: a) 12 ml of hyaluronic acid (16mg/ml , medium molecular weight), b) 8 ml of a solution comprising 2% lidocaine and and 1Ml of triamcinolone acetonide (40mg) was loaded in the device. This solution was administered continuously for three days following a arthrocentesis procedure to remove the effusion present in the joint (Figure 1).

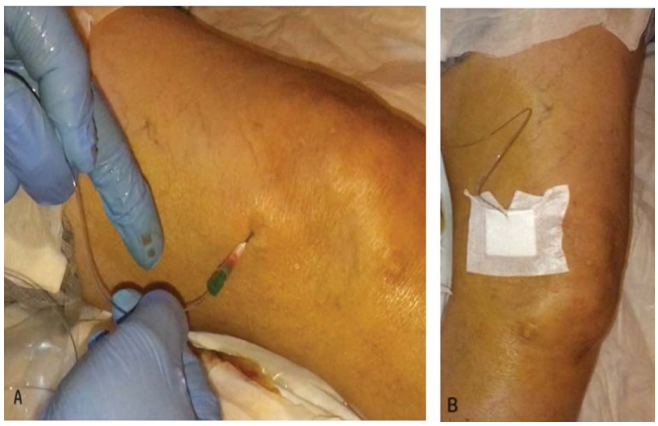

Figure 1: A: In the picture, you can see the only invasive procedure required for the installation of the device, which is a simple puncture with an 18G needle through which the catheter passes, in the non-load-bearing area of the knee. Therefore, this application is considered non-surgical and can be performed on an outpatient basis. **B:** At the end of the procedure, the patient will have a simple dressing to secure the catheter with sterile medical devices similar to those used for securing spinal catheters. This will allow the patient to move freely, positioning the device in a pouch.

The patient experienced a relevant reduction of pain lasting 12 months. The Visual Analog Scale (VAS) and Lequesne scores significantly improved compared to the level obtained by the previous conventional IA therapies. She underwent the same therapy again after one year, when became again symptomatic. She has achieved an acceptable quality of life. Additionally, there has been no further need for arthrocentesis following continuous intra-articular infusion. No adverse events were reported. The device was well tolerated on all days of application.

The implant of the device is a very safe procedure and complications should be exceptional. A small incision (about the size of a buttonhole) is made around the knee to insert the device. The type of anesthesia used by procedure is only local. The device used to give IA treatments is a thin, flexible tube that is inserted into the joint, inside the articular space. Then the small incisions is covered with a dressing. Patients need little or no pain medication. A joint catheter may stay in place for weeks and helps avoid the need for repeated IA injections (Figure 2).

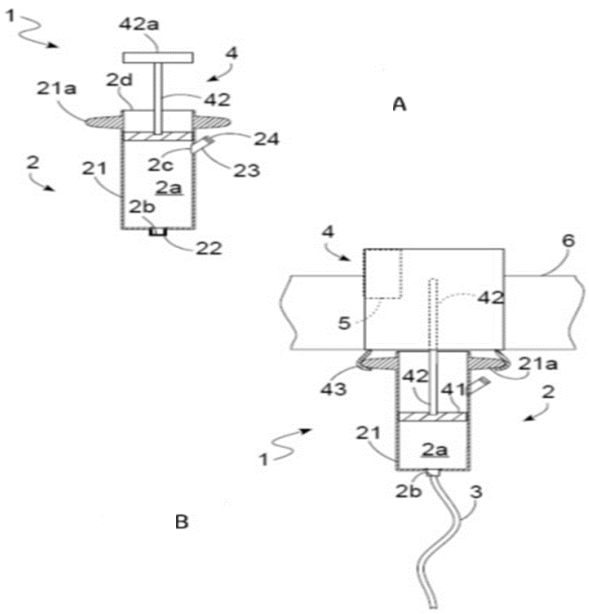

Figure 2: A: Diagram of the newly patented articular infusion device, comprising two components: A sterile consumable component including a tank (which also provides perforated access), a perforable second opening, and an infusion set. **B:** An electromechanical component that is programmable either 'on board' or via a dedicated app, featuring mechanical propulsion.

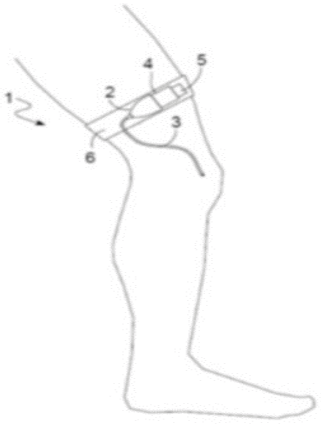

Figure 3: The device is wearable and can be used on all major joints. The simplified images depict various anchoring methods for securing the device to the patient.

Consequences of Hypothesis and Discussion

Joint catheters can resolve current problems and unmet needs. For instance, in the case of septic arthritis permanent intra-articular device can allow continuous antibiotic administration in the joint, without systemic side effects. In the case of OA, pain control, movement improvement or administration of regenerative products, can be achieved through continuous infusion. However further studies are

needed to confirm the preliminary safety results, to determine the correct indications, to distinguish the appropriate products in each clinical case and to find the proper volume and dosage to administer.

Declarations of interest

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests: the first author (S.C.) is the owner of the patent of device described in this paper.

Consent statement/Ethical approval

Not required

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Declaration of AI and AI-assisted technologies in the writing process

We did not use any kind of AI

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