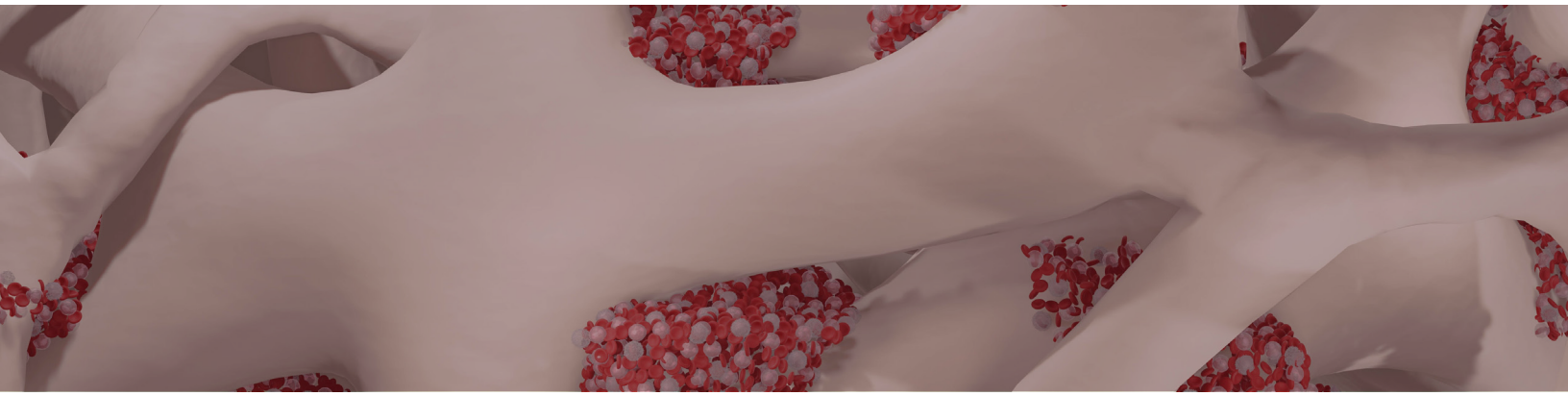
CERVOS
MEDICAL

Advancing Clinical Outcomes through Enhanced Bone Marrow Aspiration:

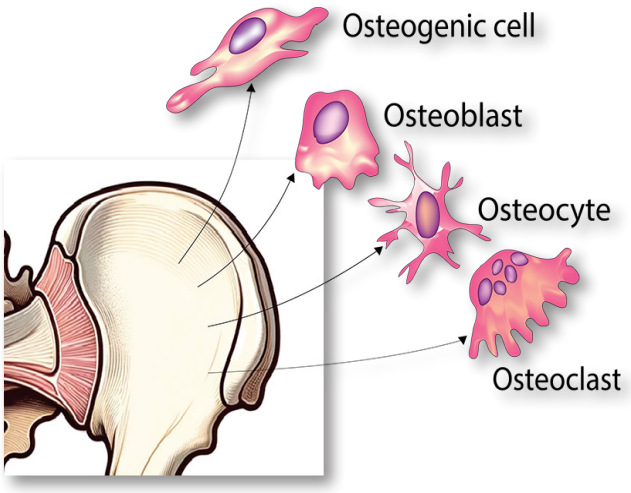
The Impact of Marrow Cellution Technology



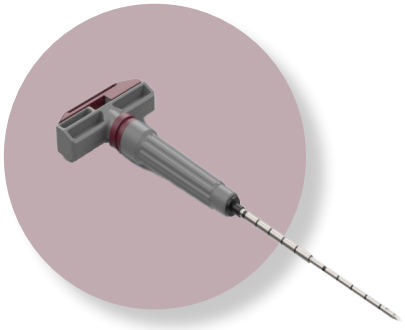
Biological characteristics of bone marrow and peripheral blood

Bone marrow, the target biologic of bone marrow aspirate, resides within the spongy tissue encased by trabecular bone. Peripheral blood, which circulates through our body, is not the intended target of marrow aspiration, yet fills the space created by the aspiration canula. Therefore, during the aspiration process, peripheral blood can fill the spaces within the marrow. This occurs due to the physical disruption caused by the aspiration needle, which creates a pathway through the bone and damages the spongy tissue's capillary network.

The primary goal during marrow aspiration is to extract the marrow fluid (BMA) from within this spongy tissue, avoiding the peripheral blood that exists outside this framework. Achieving this requires a greater suction force to be applied directly to the spongy marrow with less suction force applied to the peripheral fluid outside of the spongy marrow.

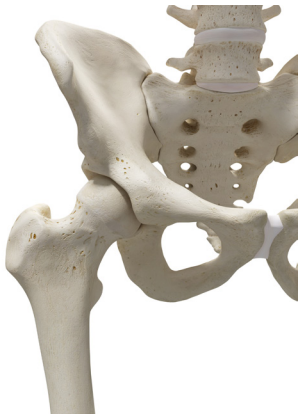


To obtain a marrow sample with improved cellular content, it's crucial to ensure that the syringe's suction is focused through the needle's apertures that are in immediate contact with the spongy marrow tissue. Once the aspiration process disrupts the capillary network within a specific area, causing peripheral blood to seep in, the needle must be moved to a new, undisturbed marrow site to continue the aspiration effectively. (5)



Physical characteristics of bone marrow and peripheral blood

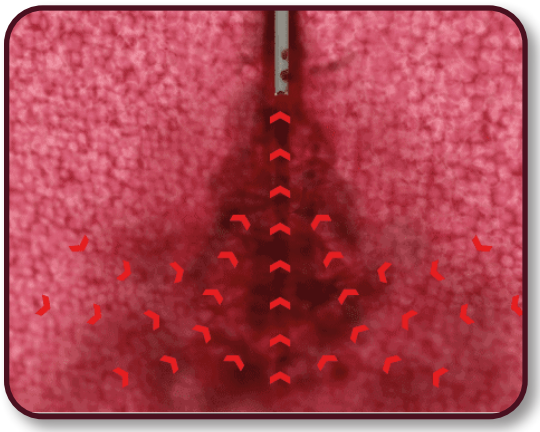
Despite their similarities, peripheral blood and bone marrow exhibit distinct physical characteristics. Bone marrow's physical location within the spongy substrate and its greater viscosity necessitates greater shear force for fluid flow movement to extract it from the dense spongy tissue. Marrow houses unique cell lineages absent in peripheral blood, features a significantly higher ratio of nucleated to total cells, and is organized into specialized geographic niches (5,6). Among these, the endosteal surface – lining the hard inner cortical surface – represents the location where the oxygen tension is lowest and the stem-like quality of the cells is greatest. This highly protected area harbors the most primitive, stem-like cells, underscoring the rich stem cell content of bone marrow as opposed to the relative scarcity in peripheral blood (1,2,3,4).



Mechanical considerations of marrow aspiration

The rigid structure of the bone cavity can trap pressure built-up by inflammation due to the insertion of the cannula (7). As the needle penetrates further into the bone, friction against the outer cannula increases from two primary sources: the cortical bone at the entry point and the inflamed, swollen tissue within the medullary space. This friction heightens the risk of the cannula becoming stuck, particularly as it is inserted deeper.

Traditional bone marrow cannula design

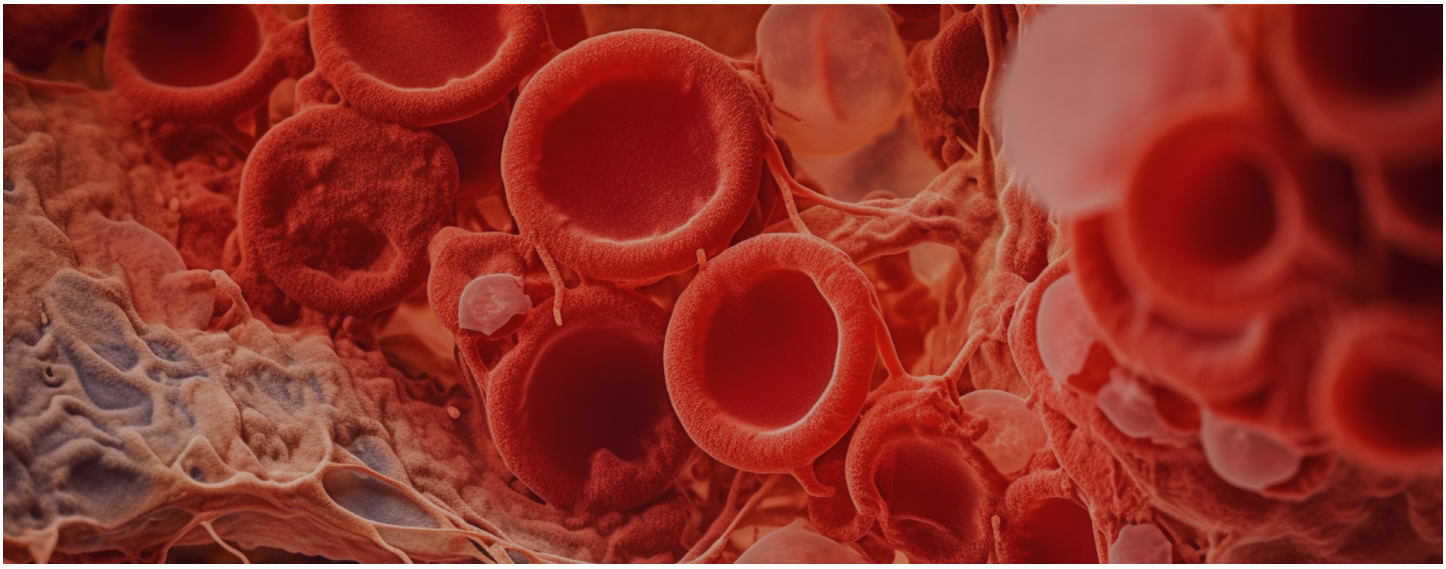


The design of a traditional bone marrow aspiration cannula features a two-component system: a hollow outer cannula and a sharp, inner stylet designed to fit snugly within it. Both the cannula and the stylet are affixed to their respective handles. This assembly allows for the separation of the components to reveal a luer hub integrated into the cannula's handle.

In practice, the combined needle, comprising both the cannula and the stylet, is inserted through the cortical bone to access the medullary cavity. Following insertion, the stylet is withdrawn, allowing for the attachment of a syringe to the cannula's luer hub. This setup facilitates the aspiration of bone marrow.

Limitations of the traditional bone marrow cannula

Risk of Lodging: The deeper the needle penetrates the medullary cavity, the more friction it encounters, increasing the risk of the cannula becoming lodged. Therefore, it's generally advised against inserting these needles too deeply into the bone to mitigate this risk.



Peripheral Blood Contamination: Each area within the marrow has a limited cell and tissue capacity. Once the available material from a location is depleted, peripheral blood invades the space, leading to contamination. The risk of cannula lodging restricts access to diverse marrow regions. Upon insertion of a traditional cannula and removal of the stylet, the cannula's end becomes open, establishing fluid communication with the luer (1-5). Although side fenestrations on the cannula may open post-stylet removal, the primary suction pressure from the syringe connected to the luer targets the cannula's open distal end. This area, near the divot left by the removed stylet, is prone to filling with peripheral blood, characterized by its lower viscosity and shear stress, facilitating easier flow compared to marrow within the spongy structure. The syringe's maximal pressure point, near the open cannula end, aligns with this area of greater flow capacity peripheral blood, thus leading to peripheral blood contamination in the aspirate.

Attempting to reposition the cannula by retracting the needle aggravates the issue as the created channel fills with peripheral blood, situated close to the cannula's main opening. Efforts to target new locations by reinserting the stylet and moving forward do not significantly improve outcomes due to the bleeding into the site that occurs from the additional time required to accomplish the protocol, and the limited insertion depth to prevent lodging, often leaving new sites too close to previous ones for an enhanced cell yield. Various approaches with a traditional cannula—such as aspirating from a single point, repositioning within the marrow, or advancing to new areas—have proven ineffective (4,8,9,10). Consequently, the less favored solution involves creating multiple cortical punctures to extract minimal aspirate volumes, a method frequently impractical for clinical applications.

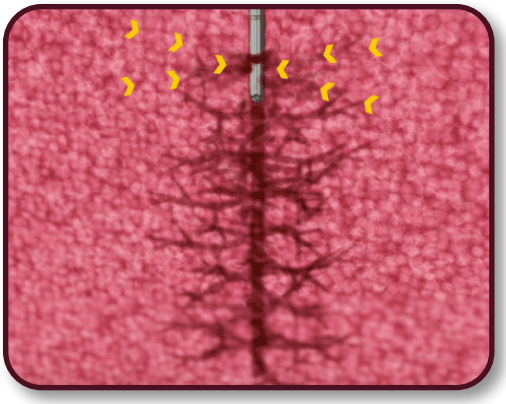
Marrow Cellution™ Technology

Marrow Cellution™ technology innovatively addresses the challenges posed by traditional bone marrow aspiration techniques. This system is distinguished by three key design features:

1. ***Blunt stylet:*** After initial entry into the medullary space, a blunt stylet replaces the traditional sharp stylet to prevent the risk of the sharp stylet exiting the space during deeper insertion, going from proximal to distal.

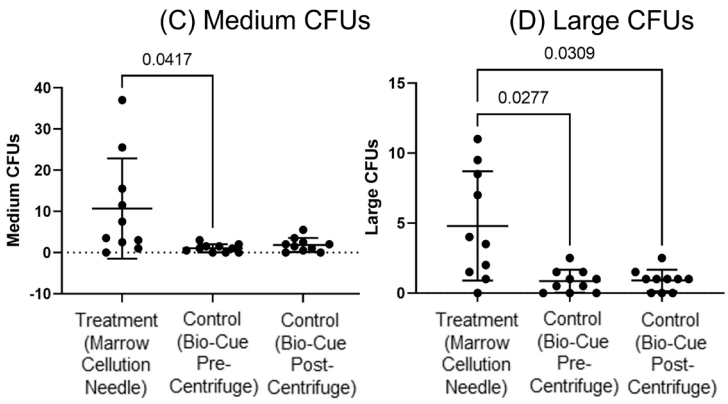
2. ***Mechanical precision:*** A unique threaded mechanical element facilitates precise and controlled movement of the cannula. This modification is crucial for relocating the cannula to unexplored marrow regions, effectively broadening the scope of accessible areas for aspiration.

3. ***Dedicated Aspiration Cannula:*** Post stylet removal, a specialized aspiration cannula is introduced coaxially through the primary introducer cannula. This secondary cannula is designed to seal the end lumen, directing the aspiration process exclusively through side apertures. This design ensures that the aspirate is predominantly sourced from the marrow, minimizing peripheral blood contamination by orienting fluid flow towards the bone's inner endosteal surface.



By integrating these innovative elements, Marrow Cellution directly counters the traditional cannula's drawbacks, offering a more effective and efficient means of bone marrow aspiration that enhances the quality and purity of the harvested material.

Comparative Stem Cell Content:
In a series of five distinct head-to-head studies, Marrow Cellution aspirate was consistently found to contain a higher concentration of stem cells than aspirates processed by conventional centrifugation techniques. Notably, in two of these comparisons, the biological samples from the Marrow Cellution group displayed superior "stem-like" qualities, such as markers indicative of small embryonic-type cells and larger colony-forming unit sizes, underscoring the enriched stem cell profile of Marrow Cellution aspirates (23,24,25,26,27).



Vascular Disorders Studies:
Marrow Cellution's efficacy was further demonstrated in two clinicalstudies focused on vascular disorders, where the Marrow Cellution group experienced significantly better outcomes than those treated with centrifuged samples, highlighting the therapeutic potential of Marrow Cellution-derived aspirates in vascular health (26,27).

"Cellular and Clinical Analyses of Autologous Bone Marrow Aspirate Injectate for Knee Osteoarthritis: A Pilot Study

Marrow Cellution delivers a significantly higher cell count..

- G. Lutz, MD"

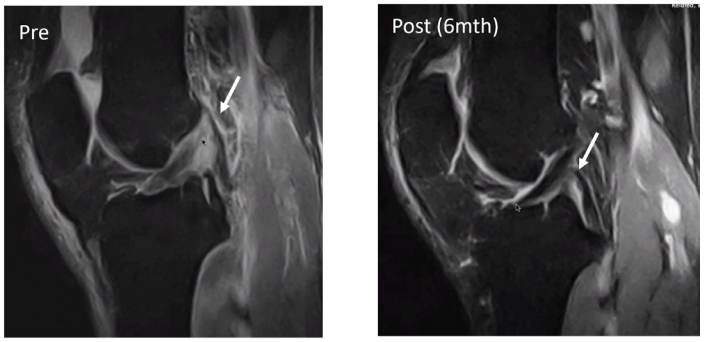
Comparison with Autograft: When evaluated against the gold standard of autografts in orthopedics, Marrow Cellution's performance was impressive. Analysis of 37 samples showed that Marrow Cellution's osteoprogenitor and nucleated cell counts were comparable, if not superior, to those of autograft samples, indicating its robust regenerative capacity (24,28,29,30,31).

Supportive Literature: The efficacy and potential of Marrow Cellution technology are further corroborated by over 17 journal articles. These publications report positive outcomes, both clinical and cellular, derived from the use of Marrow Cellution technology, contributing to a growing body of evidence supporting its effectiveness in various therapeutic contexts (23,25,27,32-45).

Patients treated with BMA have superior changes in Quick-DASH & EQ-5D-5L pain and health scores (12-month post injection) when compared to patients treated with cortisone.

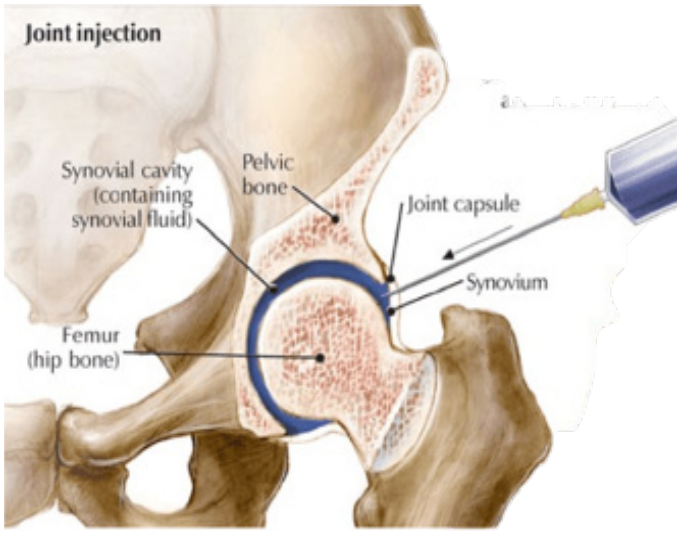
- T. Dwyer, MD

ACL Tear Marrow Cellution: RSI



Torn ACL from skiing accident. Acute injury.
Patient reports no pain that correlates to structural change in the MRI

Tim Dwyer et al. Injection of Bone Marrow Aspirate for Glenohumeral Joint Osteoarthritis: A Pilot Randomized Control Trial; Dwyer et al. Arthrosc Sports Med Rehabil 2021 Oct; 3(5): e1431–e1440



Autologous Bone Marrow Injections for Patients with Moderate Osteoarthritis of the Hip Joint.

BMA injection can provide long-term pain relief and functional restoration (as much as 6 to 12 months) for patients with hip osteoarthritis.

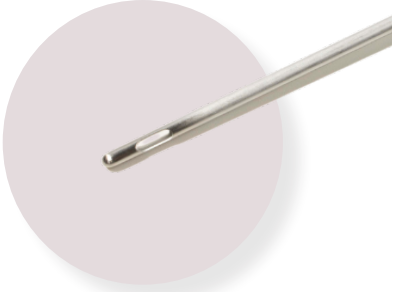
- J.R Singh, MD

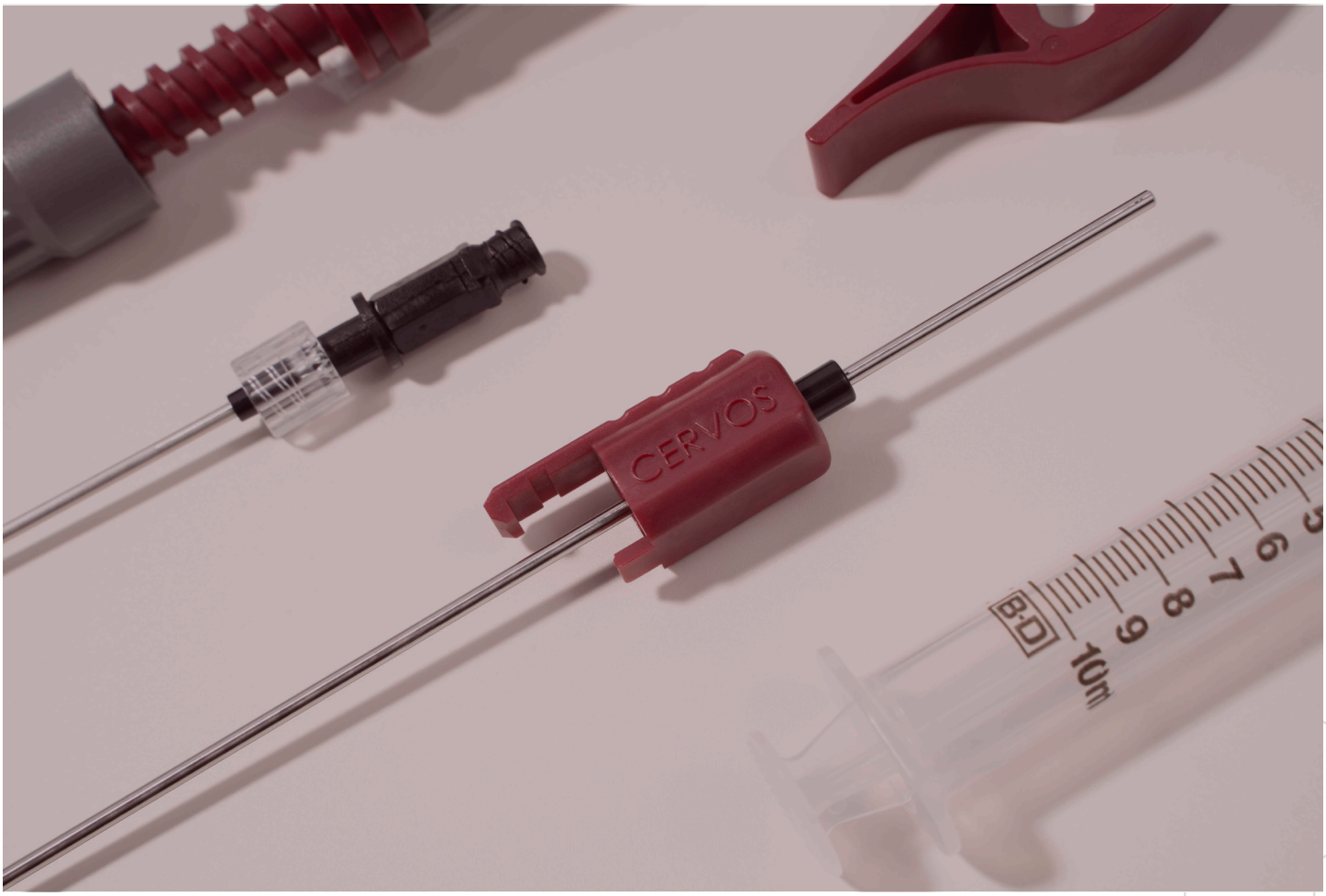
The effectiveness of any medical device is significantly influenced by the user's expertise and the application of proper techniques.

In the context of Marrow Cellution, several practices have been identified that enhance outcomes:

- Utilizing a **10 mL syringe** for aspiration ensures optimal control and precision.
- Employing a **snap-back plunger technique** enhances the consistency and quality of the aspirate.
- Limiting the volume of aspiration to **no more than 1 mL per cm of targeted marrow area** helps maintain the integrity and concentration of the cell population.
- Carefully **orienting the side apertures towards the bone's inner surface (the inner table)** optimizes the collection of high-quality marrow while minimizing peripheral blood dilution.

Adhering to these guidelines has been demo strated to improve cell counts in aspirates, underscoring the critical role of technique and training in maximizing the therapeutic potential of marrow aspiration. (30)





A Commonsense Approach

Minimizing intervention with biological materials often enhances their efficacy. Stem cells, known for their dynamic nature and prolificacy during division cycles, exemplify this principle. Prior to division, cells accumulate nucleic mass, resulting in a density surpassing that of cells typically isolated in the buffy coat layer. Crucially, many of these actively cycling cells are inadvertently discarded during centrifugation, along with the red cell layer, rather than being captured. Given that an estimated 45% of stem cells are in a state of division at any time, this biologic reality partly accounts for the low yield of stem cells retained from larger aspirates using centrifugation methods (9, 46, 47, 48). This inefficiency is a key reason hematologists/oncologists opt not to centrifuge bone marrow aspirates intended for transplant.

CERVOS MEDICAL

The Cervos Family of Products

Cervos' offerings encompass a comprehensive suite of regenerative solutions. This diverse product range is designed to provide clinicians with the flexibility to combine different biologics and delivery tools to tailor treatment approaches specific to the unique needs of each patient.

PRP (Platelet-Rich Plasma): Our advanced PRP system is engineered to maximize the concentration and viability of platelets, harnessing their growth factors and healing properties for a wide range of therapeutic applications. This system ensures a high-dose PRP preparation. Clinical outcomes are linked to dose.

Adipose: Our adipose system facilitates the efficient harvesting and processing of adipose tissue. The system includes a built-in micronizing screen, and comes with disposable infiltration and aspiration cannulas. This technology supports treatments in regenerative medicine, cosmetic and reconstructive surgery, and chronic wound management.

Bone Dowel Harvesting: Addressing the need for structural support in various orthopedic and spinal procedures, our bone dowel harvesting tools are engineered for the safe and efficient extraction of bone dowels. This addition complements our regenerative therapy solutions, offering a solid framework for cellular integration and bone repair.

Delivery Tools: To ensure precise and effective application of biologic therapies within the medullary space, Cervos offers intraosseous access cannulas. These instruments enable clinicians to accurately target treatment areas within bone.

Each component of the Cervos product family is the result of extensive R&D and physician input aimed at providing healthcare professionals with state-of-the-art tools to improve patient outcomes.

By offering a range of solutions, Cervos empowers clinicians to customize regenerative therapies based on the patient's specific condition, promoting personalized and effective treatment strategies.

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