BST-CarGel®: An Enhanced Bone Marrow Stimulation Treatment

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9.1 Introduction

Bone marrow stimulation techniques such as abrasion arthroplasty [1], Pridie drilling [2], and microfracture [3] attempt to use the natural wound repair response elicited by a blood clot originating from the bone marrow. Channels surgically made in the subchondral bone below the cartilage lesion permit access to marrow blood and blood components including stem cells intended to provide an environment for wound healing that ultimately leads to cartilage regeneration. Microfracture, which has been frequently used as a first-line treatment for small cartilage lesions, has the advantage of being simple and safe, cost-effective, and minimally invasive with a low morbidity rate [4, 5]. On the other hand, the procedure results in a mixed repair tissue with mainly fibrous or fibrocartilaginous properties [6–10], limited collagen type II and glycosaminoglycan (GAG) levels, and poor mechanical properties compared to native hyaline cartilage. Indeed, the long-term durability of this repair tissue has been questioned with many reports showing a failure of repair tissue and a return of associated clinical symptoms starting as early as 24 months post-treatment [8, 11, 12].

In an effort to guide or enhance the regeneration of more hyaline-like cartilage tissue following bone marrow stimulation, these procedures have been combined with scaffolds and/or growth factors or other biological materials [13]. These so-called enhanced bone marrow stimulation

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techniques may have the potential to overcome the main drawback of poor repair tissue quality and durability while still being safe and cost-effective, requiring a single-step, minimally invasive surgery.

9.2 BST-CarGel® Background

9.2.1 The Product

BST-CarGel® (Piramal Healthcare (Canada) Ltd.) is a new liquid scaffold that was developed to physically stabilize the blood clot in the cartilage lesion following a one-step bone marrow stimulation procedure, in order to promote hyaline cartilage formation. BST-CarGel® is based on a patented thermogel platform technology [14]. BST-CarGel® is a physiological solution (in terms of pH and osmolarity) comprised of chitosan, a buffer called β-glycerophosphate (β-GP), and hydrochloric acid (HCI). The natural biopolymer chitosan is a linear, cationic polysaccharide composed of D-glucosamine and *N*-acetyl-D-glucosamine and has been extensively studied for regenerative medicine and other biotechnological applications [15–18] due to its desirable biodegradability, biocompatibility, and mucoadhesivity.

BST-CarGel® is an implantable medical device designed to be a liquid at room temperature, mixed with fresh autologous whole blood (BST-CarGel®/blood mixture ratio of 1:3), and delivered to a cartilage lesion surgically prepared by debridement and bone marrow stimulation. BST-CarGel® is packaged as a 2-component system made up of the *Mixing Vial* (red cap) and the *Additive Vial* (blue cap) (Fig. 9.1). The *Mixing Vial* contains the chitosan solution and stainless steel beads to facilitate mixing with whole blood, while the *Additive Vial* contains the β-GP solution. The final BST-CarGel® product is obtained by combining the two solutions just prior to the addition of fresh autologous whole blood. Once the whole blood is added, BST-CarGel® is ready to be applied to the cartilage lesion where BST-CarGel® permits natural blood clotting and the in situ formation of a hybrid clot that provides a three-dimensional scaffold supporting the blood components over the marrow holes and guiding the repair process.

9.2.2 Primary Mode of Action

Many intrinsic (lesion type, location, size, and depth) and extrinsic factors (surgical technique, postoperative rehabilitation) are important in the success of a bone marrow stimulation procedure

Fig. 9.1 BST-CarGel® product packaging. BST-CarGel® is a 2-component system comprised of the *Mixing Vial* (MIX; *red cap*) and the *Additive Vial* (ADD; *blue cap*). The *Mixing Vial* contains the chitosan solution and stainless steel beads to facilitate mixing with the whole blood, while the *Additive Vial* contains the β-glycerophosphate buffer solution

for cartilage repair. The properties of the bone marrow-derived blood clot (volume, adhesiveness, and stability) and its residency in the cartilage lesion should be maximized to maintain critical blood components over the marrow channel and drive repair. Following bone marrow stimulation techniques, the loss in volume of a blood clot due to retraction can be as much as 50 % [19], resulting in a deficient healing response including a poorly filled lesion, poor tissue quality, and lack of integration of the regenerated tissue with native cartilage.

On the other hand, the mixture of BST-CarGel® with fresh autologous whole blood permits natural clot formation [20] but inhibits retraction of the fibrin scaffolding [19], thus providing a more space-filling provisional matrix for repair (Fig. 9.2). Since hyaline cartilage is

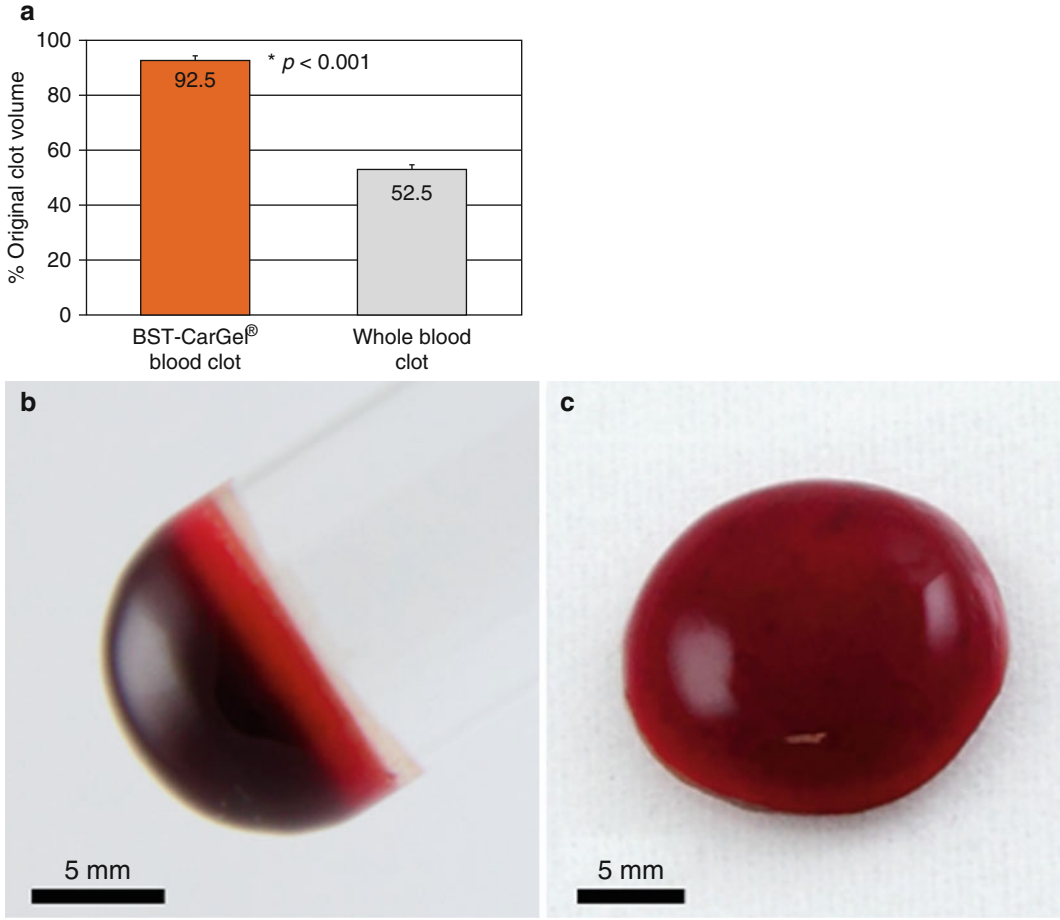

Fig. 9.2 Blood clot retraction and histology. (**a**) Clot retraction after 60 min at 37 °C was calculated from clot weights obtained before and after removal of exudated plasma ($n=25$). BST-CarGel® significantly inhibits clot retraction (92.5 % of original volume maintained) compared to whole blood only (52.5 %). (**b**) BST-CarGel®/blood clot in a glass tube and (**c**) petri dish exhibiting a bright red color, relatively little plasma exudation, and minimal retraction. (**d**) Whole blood clot in a glass tube and (**e**) petri dish exhibiting a darker red color (due to densely packed erythrocytes), plasma exudation, and significant retraction. (**f**) Histology of a BST-CarGel®/blood clot (toluidine blue staining). The chitosan (*light blue*; *empty arrowheads*) is homogenously dispersed throughout the erythrocytes (*green; black arrowheads*), and white blood cells (*dark blue*) are observed to co-localize with chitosan. The BST-CarGel®/blood clot appears less dense (less retraction) compared to the whole blood clot and does not suffer from cracking artifacts resulting from histological processing (more stable). (**g**) Histology of a whole blood clot (toluidine blue staining) demonstrating densely packed erythrocytes (significant retraction) and cracking artifacts (fragile clot)

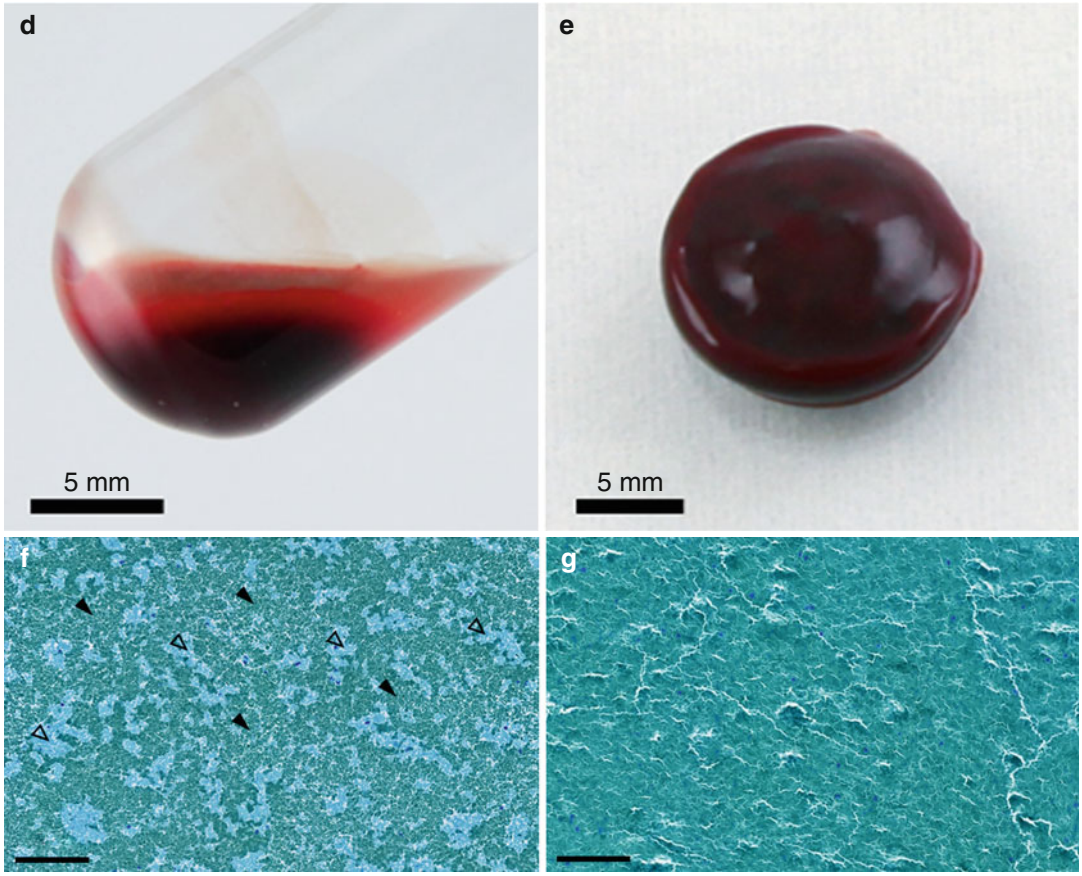

Fig. 9.2 (continued)

comprised of the negatively charged, disaccharide glycosaminoglycan (GAG) macromolecules, chitosan, the primary component of this scaffold, offers superior adhesion to the lesion surfaces due to its cationic charge [21–24]. The improved clot stabilization and adhesion brought by BST-CarGel® can easily be visualized compared to whole blood, as in Fig. 9.3. The BST-CarGel®/blood mixture provides a structurally stable and effective scaffolding with improved residency for cartilage regeneration driven by pluripotent bone marrow-derived stem cells [19–21, 23, 25]. Moreover, chitosan is biodegradable through endogenous chitosan-degrading enzymes and cells, which results in complete resorption from the implant site [14, 21, 23, 26–28].

Table 9.1 summarizes the mechanical contributions that BST-CarGel® brings in order to maximize blood clot volume and residency within a cartilage lesion.

These unique properties of BST-CarGel® result in a more voluminous implant and a prolonged residency of the BST-CarGel®/blood implant compared to the marrow blood alone, as shown in animal studies [21, 23]. These animal efficacy studies demonstrated that BST-CarGel® treatment led to (1) a greater lesion filling with a better integrated repair tissue, (2) a more cellular repair tissue with cells having a more chondrogenic phenotype, (3) an increase in glycosaminoglycan content in repair tissue (via Safranin-O staining), (4) a higher concentration of collagen type II in repair tissue (via immunohistochemistry), and (5) a more porous and vascularized subchondral bone plate [19, 21, 23].

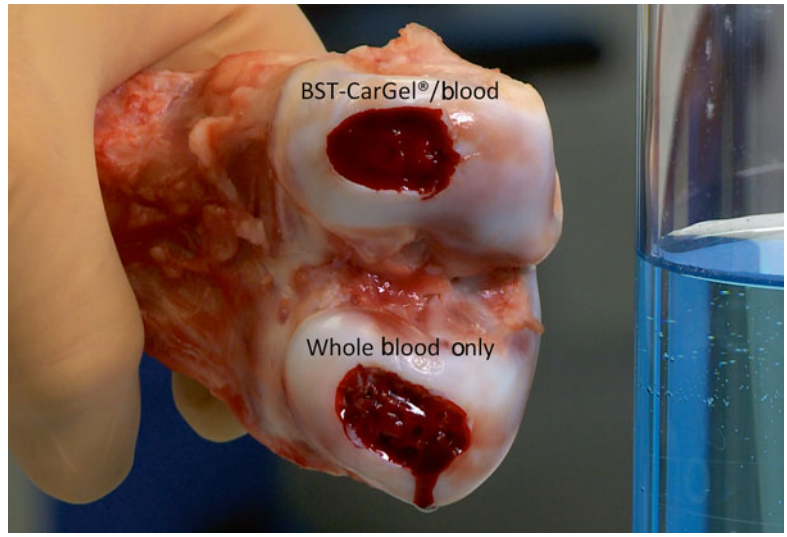

Fig. 9.3 Blood clot stabilization and increased adhesion by BST-CarGel®. BST-CarGel®/blood mixtures and whole blood were applied to microfractured lesions created on warmed pig femurs and left to clot for 15 min at 37 °C. When the femurs were then rotated to 90°, the superior adhesion of the BST-CarGel®/blood clot is observed, a result of the cationic chitosan's unique mucoadhesivity

Table 9.1 BST-CarGel®: primary mode of action

Acts as a scaffold to physically stabilize the blood clot in the cartilage lesion
Resists blood clot retraction while permitting normal clotting, thus providing a space-filling provisional matrix for repair
Adheres to the cartilage lesion surfaces

The repair processes by which the quantity and quality of repair tissue are improved by BST-CarGel® have been shown to differ significantly from those of bone marrow stimulation techniques in three enhanced healing events at early stages: (1) increased inflammatory and marrow-derived stromal cell recruitment; (2) increased vascularization of the provisional repair tissue; and (3) increased intramembranous bone formation and subchondral bone remodeling. These unique characteristics support a dynamic cartilage repair environment where resolution of the chitosan-induced wound healing leads to improved hyaline cartilage formation [21]. The development of this hyaline tissue appears to be modulated by BST-CarGel® in the timing, maturation, and position relative to articular surface of chondrogenic foci found in subchondral holes and which resemble natural cartilage growth processes [29].

The ability of BST-CarGel® to improve upon the morphology and biology of subchondral bone and the entire osteochondral unit and not just the articular surface [21, 30–32] is a critical finding as recent reviews have emphasized the important role of the osteochondral unit [33, 34]. Moreover, controversy exists regarding the potential influence of subchondral bone changes following marrow stimulation, where some reports show higher failure rates on subsequent revision surgery [35, 36] while others do not [37, 38]. The beneficial effects of BST-CarGel® on subchondral bone could potentially alleviate this issue.

9.3 BST-CarGel® Use

9.3.1 Indications/Contraindications

Correct patient profiling is an essential aspect of any cartilage repair technique. Multiple variables, as opposed to a single demographic or surgical factor, contribute to the success or failure of a given procedure. The best surgical technique, even with a proven product, can still fail if critical variables such as limb malalignment, joint instability, and obesity are not adequately assessed. If present, these contraindications for cartilage repair should be corrected, either before or concomitant with the procedure. Furthermore, lesion chronicity should also be considered since clinical outcomes, regardless of treatment, have

Table 9.2 BST-CarGel®: indications/contraindications

Indications	Contraindications
Grade 3 or 4 focal chondral or osteochondral lesions	Kissing lesions
Femoral condyles	Knee malalignment of more than 5°
Lesion area up to 7 cm^2	Meniscal insufficiencies
Traumatic or degenerative etiology	Ligamentous instability
	Shellfish allergy

been shown to be negatively correlated with chronicity [12].

Patient expectations must also be managed. Although factors such as age, activity level, comorbidities, and previous cartilage repair surgeries may have an impact on the outcome of the procedure (notwithstanding those listed above), the relative success or failure of a procedure will ultimately be judged from the patient's perspective. Consequently, it is critical for clinicians to establish the expectations of what a patient can reasonably expect for a given cartilage repair procedure based on the combination of these factors. The approach for BST-CarGel® should not differ from this.

From the current understanding of BST-CarGel® derived from the animal and clinical experience, the potential indications for BST-CarGel® are currently limited to localized or focal cartilage damage. Determining the suitability for BST-CarGel® treatment should take into account lesion grade (depth), location, and size as well as the status of the opposing chondral surface. Both traumatic cartilage damage and focal damage resulting from degenerative processes are considered indications for BST-CarGel®, the latter representing a large symptomatic patient population who are considered too young for total knee replacement. Furthermore, as already described, the mechanistic evidence from animal data has shown that BST-CarGel® has a reproducible and positive effect on subchondral bone remodeling [21, 31, 32], suggesting that cartilage loss emanating from subchondral bone pathologies, such as osteochondritis dissecans or cysts, may be addressed through BST-CarGel® treatment. A summary of indications is shown in Table 9.2 and supported by the randomized clinical trial described in Sect. 9.5.2. The presence of coexisting pathology that may adversely affect BST-CarGel®-mediated repair must be addressed before or concomitantly with the application of BST-CarGel®, including ligamentous instability, tibiofemoral malalignment, bone deficiency, patellofemoral malalignment, and meniscal pathology. The future use of scaffold-guided regenerative medicine (SGRM) using BST-CarGel® for in situ chondroinduction (ICI) can be envisioned in other joints in which chondral and osteochondral lesions are extensively found. Lesions in the ankle and hip joints might additionally be suitable for BST-CarGel® therapy because of the pathological similarities and their arthroscopic accessibility.

The approved indication for use of BST-CarGel®, according to the current labeling, is for the repair of single, symptomatic grade 3 or 4 focal cartilage lesions on the femoral condyles of the knee with an area up to 7 cm^2 in patients between 18 and 55 years old.

9.3.2 Concomitant Medications

The BST-CarGel® approach relies on the intrinsic properties of the human blood clot derived from the bone marrow, which upon clotting naturally initiates a cascade of signaling and biological events leading to wound healing through inflammatory pathways. Thus, anticoagulants and aspirin or heparin, as well as anti-inflammatory medications as tolerated, should ideally be discontinued at least 7 days prior to BST-CarGel® treatment and should not be resumed for 24 h posttreatment unless otherwise prescribed. Patients taking routine anticoagulation therapy, or when indicated, can resume their therapy 6 h after the end of the surgical procedure.

9.3.3 Surgical Technique

No unique tools or requirements in terms of facilities are needed to treat a patient with BST-CarGel® outside of a standard operating room equipped for arthroscopic surgery. A standard set of surgical instruments and retractors for open knee surgery is helpful if a mini-arthrotomy approach is used.

BST-CarGel® is applied as a viscous mixture of the product mixed on-site with fresh whole peripheral blood to a lesion which has already been debrided and treated with bone marrow stimulation (e.g., microfracture). The surgical technique for BST-CarGel® consists of three steps:

1. Preparation of the lesion through careful debridement and bone marrow stimulation
2. Preparation of the BST-CarGel®/blood mixture
3. Delivery of the BST-CarGel®/blood mixture to the lesion

Lesion Preparation

An arthroscopic probe is used to assess the targeted lesion, its limits, and the stability of its margins as well as the rest of the joint. Rough articular cartilage, flaps, and loose debris are meticulously debrided using a shaver and a curette to entirely remove the calcified cartilage layer without impinging on the subchondral bone. A contained lesion with stable vertical margins is thus created and necessary to hold the BST-CarGel® mixture adequately. Bone marrow stimulation (e.g., microfracture) is then performed as originally described [3, 4, 39]. Strict adherence to the bone marrow stimulation procedure is crucial particularly with regard to debridement and removal of the calcified cartilage considering that both noncalcified and calcified cartilage act as barriers to marrow-derived repair [40].

BST-CarGel® Preparation

BST-CarGel® should be prepared by a trained, non-sterile assistant, normally while the lesion is being surgically prepared. First, exactly 0.3 mL of the β-GP solution is removed from the *Additive Vial* using a 1 cc syringe and added slowly (at least 5 s) to the chitosan solution in the *Mixing Vial*. The mixture is then allowed to stand undisturbed for at least 10 min.

Lesion preparation and leg positioning should be performed before adding the fresh autologous whole blood to the prepared BST-CarGel®. First, 5 mL of peripheral whole blood is drawn from the patient into a plastic 5 mL syringe. Larger syringes are not recommended as they lack necessary volume gradations. Then, exactly 4.5 mL of blood is immediately added to the *Mixing Vial* using a disposable sterile hematological dispensing pin and shaken vigorously by hand for 10 s by the non-sterile assistant. A second pin is used by a sterile assistant to slowly withdraw an amount of 4–5 mL of the BST-CarGel®/blood mixture into a sterile 5 cc syringe, before handing this syringe to the treating surgeon for the delivery of the mixture into the already prepared lesion (Fig. 9.4).

Lesion Positioning and BST-CarGel® Delivery

Following bone marrow stimulation, the lesion can be accessed via an arthroscopically assisted mini-arthrotomy. The length of the incision will vary with the lesion size, but 3–4 cm usually allows sufficient visualization of the lesion to permit accurate application of the BST-CarGel®/blood mixture to the prepared lesion. Alternatively, an all arthroscopic approach is feasible if the lesion size and location allows for full visualization of the lesion and an accurate delivery of the BST-CarGel®/blood mixture. With either approach, the joint must be fully suctioned of perfusion liquid and blood, and the lesion swabbed with gauze in an attempt to create a "dry field" before applying the BST-CarGel®/blood mixture. As BST-CarGel® is implanted as a viscous mixture, the knee must be positioned such that the prepared lesion is horizontal. This position is achieved by flexing the hip and knee by approximately 90° each (Fig. 9.5) and can be maintained with the use of a Mayo table or leg holder.

The mixture is then applied to the prepared lesion in a dropwise manner using an 18G needle. The amount applied varies according to the size of the lesion. The lesion must be filled until it is almost full (Fig. 9.6). Overfilling should be avoided. The hybrid clot is allowed to solidify in place for 15 min prior to incision closure. After the 15-min solidification period, minimal manipulation of the knee and leg is essential during closing, cleaning, and wrapping. The leg should be straightened in only one motion, ensuring optimal conditions for residency of the BST-CarGel®/blood clot. A standard knee dressing is applied followed by an extension soft brace which should not be removed for 24 h after surgery.

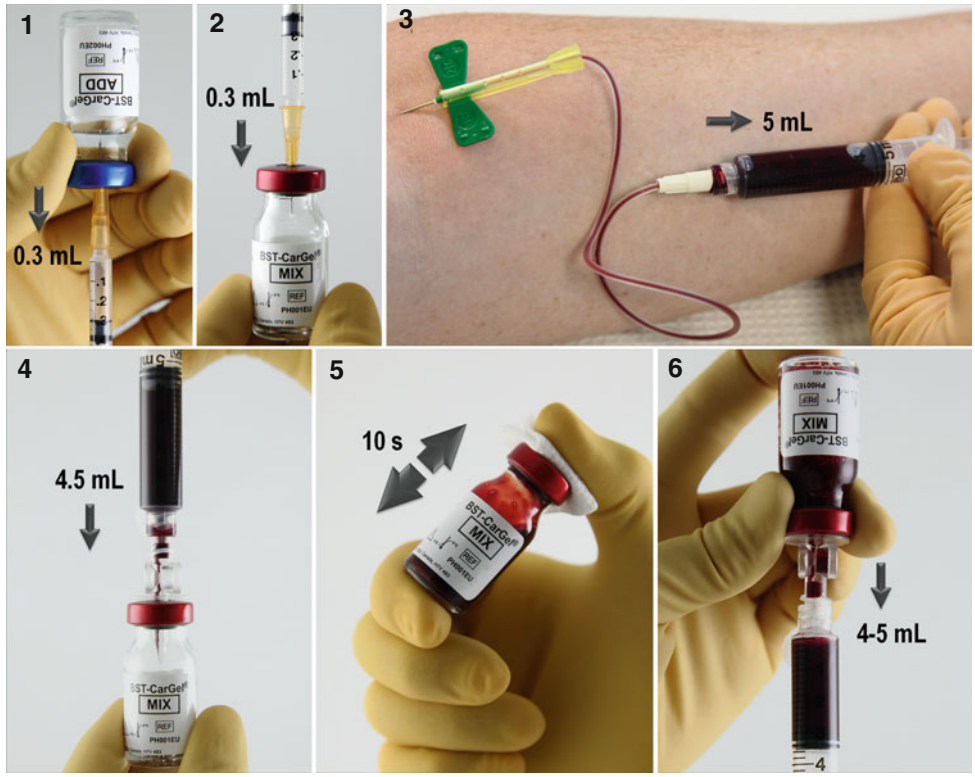

Fig. 9.4 BST-CarGel® product preparation. (*1*) The *Additive Vial* (ADD) is inverted and exactly 0.3 mL of solution (without bubbles) is removed using a sterile 1 mL syringe mounted with a sterile needle. (*2*) Taking at least 5 s, the *Additive Vial* solution is injected dropwise into the *Mixing Vial* (MIX). The *Mixing Vial* is not shaken and left upright and undisturbed for a minimum of 10 min. (*3*) When the lesion has been prepared with bone marrow stimulation, 5 mL of fresh, untreated, peripheral whole blood is collected from the patient via a peripheral vein using a 5 mL syringe. (*4*) The *Mixing Vial* septum is then wiped with alcohol before inserting a dispensing pin into the vial septum with a twisting motion. The blood-filled syringe is attached to the dispensing pin, and exactly 4.5 mL of blood is slowly injected into the *Mixing Vial*. The pin is removed and discarded. (*5*) The *Mixing Vial* is immediately and vigorously shaken for 10 s. (*6*) A second dispensing pin is inserted into the shaken BST-CarGel®/blood-filled vial and attached to a 5 mL sterile syringe. The vial is inverted and any bubbles present in the mixture are allowed to rise for 3 s. An amount of 4–5 mL of the BST-CarGel®/blood mixture is slowly drawn, being careful not to allow bubbles into the syringe. The BST-CarGel®/blood mixture is ready to be applied to the prepared cartilage lesion

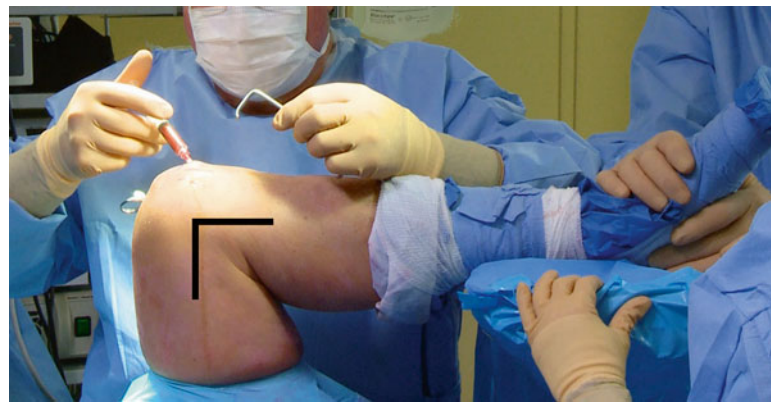

Fig. 9.5 Patient knee positioning for the delivery of BST-CarGel®. BST-CarGel® is implanted as a viscous solution, and thus the knee must be positioned such that the prepared lesion is horizontal. This position is achieved by flexing the hip and knee by approximately 90° each and can be maintained with the use of a Mayo table or a leg holder

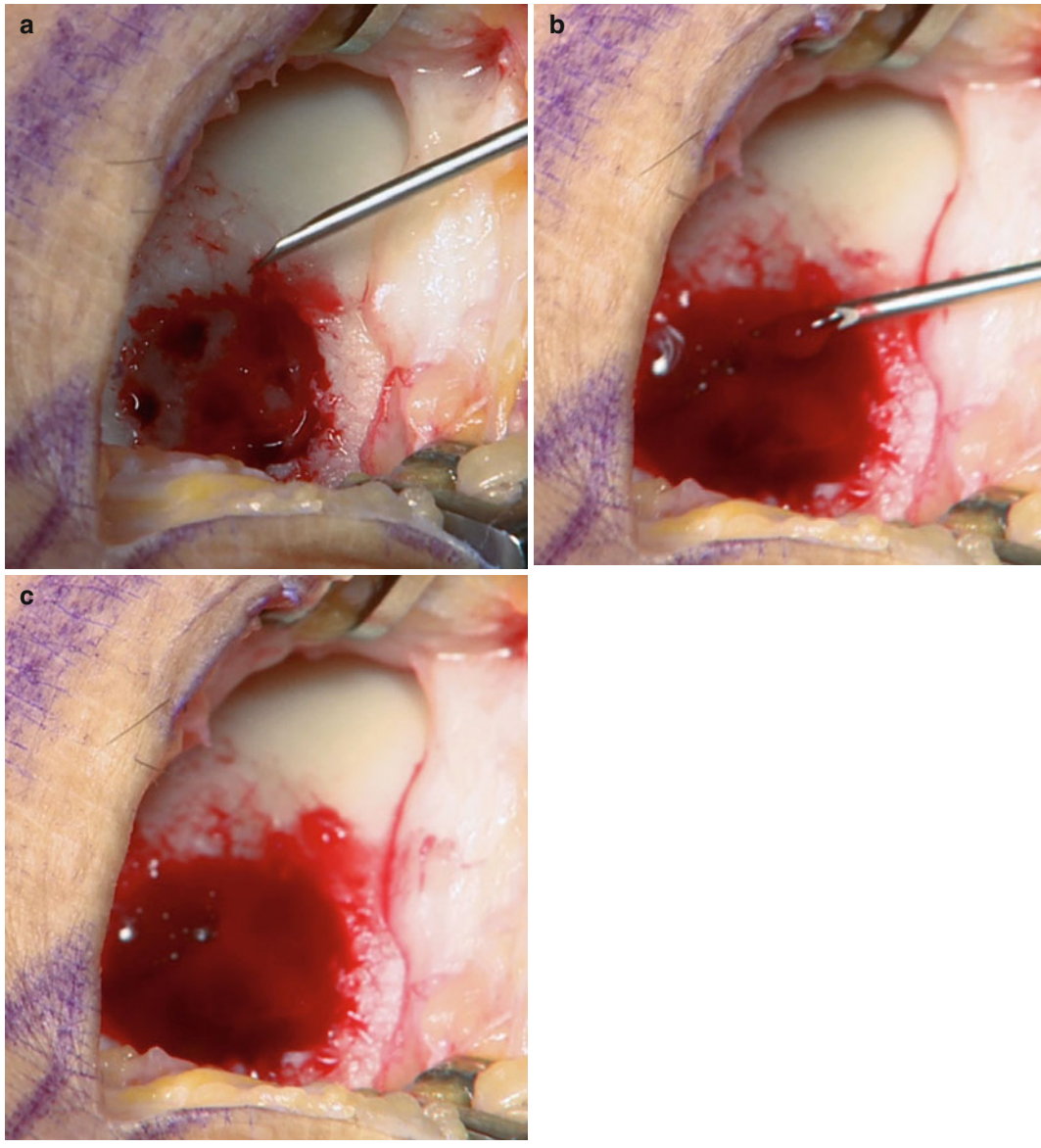

Fig. 9.6 BST-CarGel® delivery to the surgically prepared cartilage lesion. (**a**) The BST-CarGel®/blood mixture is applied to the prepared lesion (**b**) in a dropwise manner using an 18G sterile needle. (**c**) The amount applied varies according to the size of the lesion, but the lesion must be filled until it is almost full. Overfilling should be avoided. The BST-CarGel®/blood mixture is allowed to clot in place for 15 min prior to incision closure. After the 15-min clotting period, minimal manipulation of the knee and leg is essential during closing, cleaning, and wrapping. The leg should be straightened in one single motion, ensuring optimal conditions for residency of the BST-CarGel®/blood clot

9.3.4 Potential Complications and Troubleshooting

Additional points to consider with BST-CarGel® use:

- Due to the viscous liquid nature of the BST-CarGel®/blood mixture, treatment of uncontained lesions should be avoided.
- Lesions with close proximity to the notch or the origin of the posterior cruciate ligament (PCL) without sufficient containment should be avoided since rough mechanical conditions could compromise its residency.
- A second kit of BST-CarGel® should be readily available as backup in the case of over-leakage of the mixture from the lesion before

clotting, dislodgement of the implant before the straightening of the leg, or other unforeseen event or delay.

9.4 BST-CarGel® Rehabilitation

The postsurgical rehabilitation program for BST-CarGel® aims at obtaining functional recovery while protecting the developing cartilage tissue from detrimental mechanical overload. Strategically, such a program should look longer term since the maturation process during cartilage repair can last for 18–24 months or more [41, 42].

Only general guidelines are provided as the basis for the rehabilitation program, as there are other demographic and physical factors which need to be considered during rehabilitation. Such factors include patient age, weight, previous activity level, and expectations, as well as surgical factors such as lesion size and location. The basic program should then be adapted to each patient by the treating physiotherapist.

The rehabilitation program following BST-CarGel® treatment is divided into two phases: Phase 1, which generally covers week 1–8 postoperative, and phase 2, which is intended for a full weight-bearing longer-term follow-up for weeks 9–26 postoperative. Table 9.3 lists the rationale and suggestions for modalities to be used.

For phase 1, immediately following surgery, the joint is completely immobilized for the first 24 h with a soft brace in extension which is then used for 14 days during all movement and at night. Frequent sessions with an experienced therapist are desired in phase 1, up to five times for the first week and three times per week for the remaining weeks. Assisted passive motion exercises are used to maintain mobility, increase range of motion, and ensure overall knee health while initiating the mechanical signaling which will modulate the tissue development. Once 110° of flexion is obtained, stationery cycling is permitted. Weight bearing is not allowed for the first 6 weeks, and from week 6–8 the goal is to reach full weight bearing as pain allows. Other standard modalities can be implemented as per therapist preference as shown in Table 9.3. Once the objectives of the phase 1 are attained, the patient can move to phase 2.

Phase 2 implies a normal use of the involved knee joint for activities of daily living, excluding sports-related activities. Strengthening with closed chain kinetic exercises can be implemented to obtain the goals shown in Table 9.3. At the end of this phase, patients are encouraged to begin light sport activities like cycling or swimming. Higher impact or contact sports which involve pivoting are not permitted to resume before 1 year postsurgery, as the maturing tissue is still vulnerable to mechanical loading.

Table 9.3 BST-CarGel® rehabilitation program

Rationale		Modality
Phase 1: 1–8 weeks	Protect and maintain implant residency	6 weeks non-weight bearing
	Control knee pain and swelling	Day 2–7: passive ROM, <35° flexion
	Regain normal range of motion	Day 8–28: passive ROM as tolerated
	Stimulate the new cartilage tissue	Neuromuscular stimulation
		Isometric quad/hamstring contraction
		Hip strengthening
		TheraBand®
Phase 2: 9–26 weeks	Obtain full range of motion	Proprioception exercises with pain-free full weight bearing
	Stimulate maturation of new cartilage tissue	Progressive closed kinetic chain exercises
	Ensure a normal gait pattern	Balance board
	Strengthen muscles and normalize proprioception	Calf raise with progression to unipodal calf raise
	Reinitiate light sport activities (no impact)	Cardiovascular exercise (cycling, walking, swimming, StairMaster) at least 20 min/day

9.5 BST-CarGel® Clinical Experience

9.5.1 Pilot Use

Pilot clinical use of BST-CarGel® occurred from August 2003 to December 2004 under Health Canada's Special Access Program for medical devices intended for compassionate use. Thirty-three patients were treated with BST-CarGel® and encompassed the spectrum of indications, with both traumatic and degenerative lesions, where lesions ranged in size from 0.5 to 12 cm^2 (mean area 4.3 cm^2) for both men and women. One case of osteochondritis dissecans and one exposed subchondral cyst were also treated. Concomitant anterior cruciate ligament replacement preceded treatment with BST-CarGel® in two patients. BST-CarGel® was delivered by arthroscopy for 22 patients and by mini-arthrotomy for 11 patients. This clinical experience is recognized as observational and uncontrolled, but it still yielded an initial assessment of safety as no uncharacteristic observations were made during physical examinations or blood analyses for all patients. At 12 months postoperatively, Western Ontario McMaster (WOMAC) Osteoarthritis Index questionnaires for pain, stiffness, and function improved compared with preoperative baseline scores, and the uniformity of the WOMAC data indicated a clear clinical benefit arising from BST-CarGel® treatment. In addition, surgical experience gained with BST-CarGel® was used to support the development of the clinical protocol for the international multicenter randomized clinical trial described in the following section.

9.5.2 BST-CarGel® Randomized Clinical Trial

A regulated international multicenter trial was performed in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice (GCP) to evaluate BST-CarGel® efficacy at 12 months in repairing cartilage lesions and improving patient clinical symptoms, compared to microfracture, the current standard of care. The trial was conducted in 26 clinical centers in Canada, Spain, and South Korea. Eligible male and female patients were 18–55 years of age with an isolated grade 3 or 4 cartilage lesion on the medial or lateral femoral condyle and moderate knee pain (>4 VAS). Patients had stable knees with intact menisci, BMI ≤ 30 kg/m^2, and had not undergone previous cartilage or ligament treatments in the study knee within 1 and 2 years of baseline, respectively. The trial enrolled 80 patients, who were randomized (1:1) at the time of surgery to BST-CarGel® or microfracture alone treatment groups, and followed standardized 12-week rehabilitation. This trial represents the first of its kind in cartilage repair using a novel, three-dimensional quantitative MRI to compare repair cartilage structure through standardized data acquisition and blinded analyses for the co-primary endpoints of quantity and quality of new cartilage tissue. The degree of cartilage lesion filling (lesion % fill) was calculated volumetrically at 12 months as a percentage of the 1 month postoperative lesion baseline and a collagen-based quality parameter was measured at 12 months using the transverse (or T2) relaxation time of the entire volume of new tissue. Secondary endpoints at 12 months included clinical benefit, determined with WOMAC questionnaires, and safety. Supportive data from 38 elective biopsies retrieved at 13 months included International Cartilage Repair Society (ICRS) macroscopic scoring (during retrieval), blinded ICRS I and II histological assessments, and polarization light microscopy (PLM) score for collagen architecture.

BST-CarGel® treatment met both co-primary trial endpoints by achieving statistical superiority over microfracture in both the degree of filling of treated lesions and the quality of the new tissue. The data revealed that compared to the microfracture group, the BST-CarGel®-treated lesions contained a significantly greater volume of repair cartilage which exhibited a more ordered collagen structure by T2 than that of microfracture, with characteristics approaching that of native hyaline cartilage. WOMAC assessments for pain, stiffness, and function yielded equivalent and statistically significant improvements from baseline for both groups. Safety was comparable for both

groups. Compared to microfracture, BST-CarGel® showed improved ICRS macroscopic grading, superior collagen organization by PLM, and improvements in most ICRS I and II histological parameters.

Overall, BST-CarGel® treatment resulted in greater lesion filling and superior repair tissue quality at 12 months as shown by multiple, independent indicators. Such striking structural improvement should be predictive of longer-term durability of repair and sustained clinical benefit compared to microfracture.

BST-CarGel® has only been approved for sale in Europe at this time.

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