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Review Article
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Biopuncture, A Multitarget Therapy in the Treatment of Individuals with Knee Osteoarthritis: state of the art

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Background: Biopuncture is a described technique that consists in subcutaneous injection of antihomotoxic drugs (homeopathic compounds) mixed with other substances such as local anesthetics or dextrose; This has been proposed as a treatment option to reduce musculoskeletal pain in various locations, including knee osteoarthritis.
Objectives: The objective of this manuscript was to carry out a comprehensive review of the published information on the use of Biopuncture in patients with knee osteoarthritis.
Methods: A scientific search was performed using online databases following the terms (Biopuncture) and (Knee Osteoarthritis) to identify scientific manuscripts that were related to the use of Biopuncture in the treatment of individuals with knee osteoarthritis.
Results: With the information found, a theoretical framework was integrated that describes the components of Biopuncture, its mechanism of action and practical topics for the application of the technique.
Conclusion: Biopuncture appears to be a potential, simple and low-risk therapeutic strategy in the treatment of knee osteoarthritis, which is applied through periarticular subcutaneous injections, with multitarget mechanisms of action at various physiopathological levels such as the modulation of the inflammatory process, decreased peripheral sensitization, and stimulation of antidegenerative and trophic mechanisms. Perhaps it can be part of the integrative treatments for knee osteoarthritis.

Keywords: antihomotoxic medicine, biopuncture, knee osteoarthritis

INTRODUCTION

The knee joint is the most common site of osteoarthritis [1], which is one of the main causes of pain and mobility limitation [2]. Knee osteoarthritis (KOA) mainly affects the cartilage and subchondral bone; however, it also involves other joint tissues, including the ligaments, menisci, joint capsule, and synovium. Some of these joint tissues have a high concentration of nociceptors; therefore, the pain that often accompanies KOA can be attributed to inflammation, sensitization, and degeneration of the richly innervated intra-articular and periarticular tissues [2, 3]. General recommendations for treating KOA include nonpharmacological therapy, pharmacological treatment, and interventional measures (such as intra-articular injections of corticosteroids or hyaluronic acid) [4, 5]. Other emerging therapies include intra-articular injections of hypertonic dextrose [6, 7], ozone [8], or platelet-rich plasma [9] that can target intra-articular structures. In addition to intra-articular injections, treatments that only involve periarticular procedures, (such as periarticular injections of local anesthetics [10] or dextrose [11]) have been used for pain control in individuals with KOA.

Biopuncture is another treatment option in individuals with KOA. It involves the injection of antihomotoxic drugs (homeopathic compounds) mixed with other substances, such as local anesthetics or dextrose. Biopuncture has been proposed as a treatment option to reduce musculoskeletal pain in various locations [12]; however, little information on it is available so far.

In this study, we performed a comprehensive review of pub-

lished information on the efficacy of biopuncture (using antihomotoxic drugs mixed with local anesthetics and dextrose) in individuals with KOA. We aimed to develop a theoretical framework that explains the components of biopuncture, its mechanisms of action, and practical considerations for its application.

MATERIALS AND METHODS

A search was performed using online databases, such as the National Library of Medicine (MEDLINE/PubMed), Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Scientific Electronic Library Online (SciELO) databases, for literature published up to December 2023. Moreover, other sources, such as Google Scholar and gray literature, were included in the search to identify documents that could be useful but were not included in the aforementioned databases. Various search strategies and keywords were used to include as much information as possible on the topic. The primary search included the following terms: (biopuncture) and (knee or knee osteoarthritis). The secondary search was performed using multiple combinations of the following terms closely related to biopuncture: (antihomotoxic medicine or antihomotoxic drugs or Trameel or Traumeel or Tr14 or Zeel or Zeel T or Ze14 or Lymphomyosot or dextrose injection or local-anesthetic injection) and (knee or knee osteoarthritis). A direct search was also performed using the bibliography referenced in the identified documents to identify documents that could be useful and were not found in the database.

RESULTS

1. Search and compilation

A total of 7,780 citations were identified. In our primary search, only 39 documents were found in which biopuncture was used for the treatment of individuals with KOA. Moreover, in our secondary search, when terms closely related to biopuncture were included, 7,741 documents were identified. After eliminating duplicate documents and those in which the components of biopuncture were used for treating pathologies other than KOA, 476 documents in which the components of biopuncture were separately used for the treatment of KOA were reviewed. These included preclinical studies conducted in vitro or using animal models, clinical studies, reviews, editorials, theses, books, and published abstracts. Complete search strategies for each database are found in Supplement 1.

Using the information that was found and extracted, a theoretical framework was integrated, explaining the components of biopuncture, its mechanisms of action, and practical considerations for its application.

2. Definition and components of biopuncture

The term biopuncture was coined by a Belgian doctor, Jan Kersschot, to describe a therapeutic technique that consists of the injection of a mixture of antihomotoxic drugs (homeopathic compounds), local anesthetics, and dextrose via the subcutaneous, local intramuscular, periarticular, perineural, or perilesional route. His objectives were to modulate the inflammatory process and to induce or accelerate the regeneration–repair process [12, 13]. This technique is based on the combination of other therapeutic procedures, such as antihomotoxic medicine, neural therapy, Hackett–Hemwall prolotherapy, subcutaneous perineural therapy (neural prolotherapy), and mesotherapy [12].

Antihomotoxic drugs are considered compound homeopathic drugs that contain a combination of peptides of herbal, mineral, and/or animal origin diluted to low concentrations (homeopathized) [14]. These drugs are used for treating musculoskeletal pain [15]. Various companies produce these drugs for oral administration and injections in vials [13]. Among these, the best-known drugs are Traumeel, Zeel, and Lymphomyosot [15, 16]. Traumeel includes a combination of 14 homeopathized mineral and vegetable substances (Arnica D2, Calendula D2, Chamomilla D3, Symphytum D6, Millefolium D3, Belladonna D2, Aconitum D2, Bellis perennis D2, Hypericum D2, Echinacea angustifolia D2, Echinacea purpurea D2, Hamamelis D1, Mercurius solubilis Hahnemanni D6, and Hepar sulfuris D6). It has been used for more than 60 years for the treatment of musculoskeletal injuries and marketed in more than 50 countries as a compound homeopathic drug [17, 18]. Zeel is an antihomotoxic drug that consists of a combination of 14 diluted substances of mineral, vegetable, and animal origins (Cartilago suis D6, Funiculus umbilicalis suis D6, Embryo suis D6, Placenta suis D6, Solanum dulcamara D3, Symphytum D6, Nadidum D8, Coenzima A D8, Sanguinaria canadensis D4, Natrium oxalaceticum D8, Acidum α-liponicum D8, Toxicodendron quercifolium e summitatibus rec. D2, Arnica montana D4, and Sulfur D6). It is indicated for treating degenerative joint disease and other arthropathies [19]. Lymphomyosot includes a

combination of 17 substances of vegetable and mineral origins (Myosotis arvensis D3, Veronica D3, Teucrium scorodonia D3, Pinus sylvestris D4, Gentiana lutea D5, Equisetum hyemale D4, Sarsaparilla D6, Scrophularia nodosa D3, Juglans regia D3, Calcium phosphoricum D12, Natrium sulfuricum D4, Fumaria officinalis D4, Levothyroxinum D12, Aranea diadema D6, Geranium robertianum D4, Nasturtium aquaticum D4, and Ferrum jodatum D12). In antihomotoxic medicine, it is used to stimulate lymphatic tissue drainage, thereby treating edema and inflammation [15, 20]. These drugs are regularly used in clinical practice. Injectable antihomotoxic drugs represent a therapeutic option for individuals with musculoskeletal injuries because they exhibit positive effects comparable to those of nonsteroidal anti-inflammatory drugs (NSAIDs), albeit with fewer side effects. Moreover, the level of scientific evidence that supports their use is highly acceptable [21].

Local anesthetics are also frequently present in biopuncture solutions [12, 16, 22]. The injection of local anesthetics is a therapeutic intervention that has long been used for treating neuromusculoskeletal pain [23, 24]. The underlying mechanism of action involves the blocking of nociceptors and sensory fibers, thereby modifying peripheral sensitization processes [10, 23], which are common in the pathophysiology of musculoskeletal pain [3, 25]. Moreover, local anesthetics exhibit certain anti-inflammatory properties [26, 27]. In biopuncture, local anesthetics (e.g., lidocaine or procaine) are used in low concentrations (generally up to 0.2%) [12, 16, 22]. Unlike neural therapy, biopuncture does not have neuroganglial or intravasal applications [12]. Biopuncture seeks to exhibit a desensitizing effect without causing cellular cytotoxicity, which can inhibit the repair–proliferation process [12]. Low concentrations of local anesthetics are used because high concentrations have been reported to cause cytotoxicity in tenofibroblast and chondrocyte cultures [28, 29].

At times, dextrose is also included in the biopuncture mixture [12, 16, 22]. The use of dextrose injections is becoming increasingly common for treating neuromusculoskeletal pain. Dextrose is used in different techniques, such as Hackett–Hemwall prolotherapy [30], hydrodissection [31], and subcutaneous perineural therapy [32]. Hackett–Hemwall prolotherapy consists of injections of hypertonic dextrose (at concentrations ranging from 12.5% to 25%) in the ligament–bone system, tendon–bone system, or intra-articular space. This initially induces a proinflammatory response and eventually induces a proliferative response that facilitates tissue repair [30, 33]. A recent meta-analysis reported that the efficacy of prolotherapy with hypertonic dextrose was comparable to that of intra-articular injections of hyaluronic acid in individuals with KOA [7]. Subcutaneous perineural therapy was first described by Dr. Lyftogt for treating chronic musculoskeletal pain [32]. It consists of subcutaneous injections of 5% dextrose in areas that follow the trajectory of superficial sensory nerves, especially on spots where nerves cross the fascial layers [34]. In biopuncture, dextrose is used as a therapeutic substance at concentrations of 5%–10%; higher concentrations are not used to prevent a proinflammatory effect and avoid discomfort during and after application, making it different from Hackett–Hemwall prolotherapy. Moreover, in biopuncture, dextrose can be applied not only to the constriction sites of the superficial sensory nerves but also to periarticular areas, making it different from subcutaneous perineural therapy [12].

3. Mechanisms of action

Biopuncture represents a multitarget therapeutic approach for the treatment of musculoskeletal pain. As it contains several components, its effectiveness can be attributed to various mechanisms of action. Some of the proposed mechanisms of action are as follows:

1) Inflammatory mechanisms

Biopuncture may have an important modulatory effect on inflammation because of the effects of antihomotoxic drugs, such as Traumeel and Zeel [14, 15], and the anti-inflammatory properties of local anesthetics [26, 27].

In vitro and animal model studies have reported that Traumeel modulates the release of different inflammatory mediators, reducing the production of interleukin-1 beta (IL-1β) by 70%, tumor necrosis factor-alpha (TNF-α) by 65%, and interleukin-β (IL-β) by 50% in lymphocyte cultures [35]. Moreover, clinical studies have reported that Traumeel exhibits a favorable effect on various musculoskeletal pathologies and represents an alternative to NSAIDs for the treatment of acute or chronic musculoskeletal pathologies [36, 37].

Similarly, in vitro studies have reported that Zeel downregulates the synthesis of leukotrienes and prostaglandins in activated human leukocytes [38], which could have an important anti-inflammatory effect. Lozada et al. [39] conducted a clinical trial and reported the efficacy of intra-articular injections of Traumeel and Zeel in controlling pain and improving function

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in individuals with KOA.

The anti-inflammatory effect of antihomotoxic drugs can be potentiated by the anti-inflammatory properties of local anesthetics at low doses, as they reduce vascular permeability, proinflammatory cytokine release, neutrophil adhesion, and enzyme release [26, 27]. This could serve as an interesting therapeutic synergy.

2) Desensitizing mechanisms

Peripheral sensitization plays an important role in the genesis and perpetuation of musculoskeletal pain, including pain in individuals with KOA [2, 3, 25]. It involves the amplification of the pain signal produced by nociceptor hyperreactivity, which translates into an increased intensity of pain and/or changes in its topographic distribution that are generally caused by the release and accumulation of proinflammatory cytokines in the injured tissue [25]. According to their mechanisms of action, both local anesthetics and dextrose can lower the reactivity of nociceptors, thereby reducing peripheral sensitization.

It has been proposed that the blockade of nociceptors and sensory fibers caused by the injection of local anesthetics in the affected tissue reduces the discharge threshold of nociceptors, thereby reducing the processes of peripheral sensitization. Therefore, periarticular injections of local anesthetics have been used to control pain in individuals with KOA [23].

On the other hand, it has been proposed that subcutaneous infiltrations of dextrose have analgesic mechanisms of action associated with desensitizing effects, such as the blockade of TRPV-1 ion channels [32], activation of the alpha 3 fraction of the inhibitory glycine receptor (GlyR) [40], activation of K^+ channels (TREK channels) [41], and activation of acid-sensitive ion channel 1a (ASIC1a) [42]. These mechanisms are related to the inhibition of neurogenic pain transmission. The subcutaneous application of dextrose has effectively reduced pain in individuals with joint pathologies, such as KOA [43, 44], and in postoperative KOA cases [45].

The effects of local anesthetics and 5% dextrose may be synergistic [46]. Moreover, the desensitizing effects of local anesthetics and dextrose could be potentiated by the antihomotoxic drug Lymphomyosot, which enhances the cleansing effect of connective tissue [15] by increasing local lymphatic drainage [20, 47], favoring the drainage of proinflammatory mediators and sensitizing substances accumulated in the tissue.

3) Antidegenerative and proliferative mechanisms

Biopuncture could also have antidegenerative and proliferative effects because of the actions of dextrose and drugs, such as Traumeel and Zeel. In vitro studies have reported that dextrose exhibits an antidegenerative effect on cartilage by decreasing the function of metalloproteinase (MMP) 1 [48]. Similarly, basic and animal model studies have reported that dextrose promotes collagen deposition and increases the cross-sectional area of treated ligaments and tendons [49, 50], in addition to exhibiting a trophic effect on cartilage [51, 52]. Trophic effects on cartilage have also been reported in humans [53]. Although these proliferative effects have been attributed to hypertonic concentrations of dextrose (> 12.5%) [30], dextrose concentrations lower than 10% can also have proliferative effects on ligaments [54].

The antidegenerative/proliferative effects of dextrose could be enhanced when combined with drugs, such as Traumeel or Zeel. Traumeel reduces MPP 13 activity in chondrocyte culture by 30%, increases the production of glycosaminoglycans, and stimulates the production of transforming growth factor beta (TGF-β) [55], while Zeel increases the in vitro response and activity of articular chondrocytes by 25% [56]. Various clinical studies have reported the efficacy of periarticular and/or intraarticular injections of Zeel in controlling pain and improving function in individuals with KOA [39, 57, 58].

4. Practical considerations for the application of biopuncture in individuals with KOA

1) Preparation of the biopuncture mixture

The components of the biopuncture mixture should exhibit a multitarget effect in individuals with KOA by modulating the inflammatory process, promoting the desensitization of periarticular tissues, and stimulating antidegenerative and trophic mechanisms in tissues. Therefore, the biopuncture mixture consists of a combination of local anesthetics (such as lidocaine or procaine), dextrose, and antihomotoxic drugs (such as Traumeel, Zeel, or Lymphomyosot) [12, 13, 16].

In biopuncture, local anesthetics (e.g., lidocaine or procaine) are used in low concentrations (generally up to 0.2%), and dextrose is used in concentrations below 10% [12, 16, 22]. Therefore, it has been recommended to prepare a mixture of these substances with antihomotoxic drugs to achieve the required dilution [12, 16]. A practical way of complying with these recommendations is to prepare the biopuncture mixture in a 10 mL

syringe. The following components should be added:

- Add 2 mL of dextrose at 50% concentration. Thus, the final concentration of dextrose will be 10%, which is sufficient to promote desensitization mechanisms [25, 40-42] and proliferative and antidegenerative mechanisms [52, 54] without exhibiting a proinflammatory effect.
- Add 1 mL of lidocaine or procaine at 2% concentration. The final concentration of the local anesthetic will be 0.2%, which is sufficient to modulate nociceptor hyperactivity [10] and exhibit anti-inflammatory effects [26, 27].
- Add 1 mL of Traumeel, which exhibits anti-inflammatory [35], antidegenerative, and proliferative effects [55].
- Add 1 mL of Zeel, which exhibits anti-inflammatory [38] and proliferative [56] effects.
- Add 1 mL of Lymphomyosot, which promotes the cleansing effect of connective tissue by increasing local lymphatic drainage [20, 47].
- Add 4 mL of 0.9% saline solution as a diluent.

According to the biopuncture application scheme for KOA, two syringes equipped with 27- or 30-gauge × 1/2-inch needles and containing 10 mL of this mixture will be required to treat one knee.

2) Biopuncture application scheme for KOA

For biopuncture, injections can be administered via the following points: transdermal (mesotherapy type), subcutaneous, periarticular, local intramuscular (trigger points), and acupuncture [12-15, 22]. Intra-articular application is not a primary part of the biopuncture application scheme.

In the biopuncture application scheme, the subcutaneous route is the most common [12, 22] because of its ease of application and very low risk of complications. Although intra-articular treatments directed toward cartilage and intra-articular structures as target tissues are frequently used in individuals with KOA [59], subcutaneous treatments may have good therapeutic effects on the superficial periarticular tissues of the knee [10, 43, 44, 57]; some tissues are located just below the subcutaneous tissue and participate in the genesis of pain in individuals with KOA through mechanisms of inflammation, sensitization, and degeneration [2, 3]. Individuals with KOA could be susceptible to the therapeutic effects of the substances used in biopuncture when these are applied subcutaneously. Moreover, the subcutaneous route may affect deeper joint structures. In the study of Sota Omoigui et al. [60], on administering subcutaneous injections with 30-gauge needles, jet ejection was observed (reaching a depth of 4–6 cm, as measured by ultrasound). This suggests that a simple subcutaneous injection could reach deeper structures.

The biopuncture application scheme for individuals with KOA may include various anatomical points around the knee for subcutaneous application. Some strategic points and application doses are mentioned below (Fig. 1):

1. A point on the most proximal edge of the medial femoral condyle: This point coincides with the proximal insertion of the medial collateral ligament and the emergence of the superior medial genicular nerve [10, 61-63]. It coincides with the SP-10 acupuncture point [43]. Here, 2 mL of the biopuncture mixture should be applied (Fig. 1A).
2. A point at the medial joint line level: This point coincides with the coronary ligaments of the medial meniscus [63] and with the passage of branches of the superior medial genicular nerve [10, 62]. It coincides with the LV-8 acupuncture point [43]. Here, 2 mL should be applied (Fig. 1A).
3. A point on the most distal edge of the medial tibial condyle: This point coincides with the distal insertion of the medial collateral ligament, the insertion of anserine tendons, and the emergence of the inferior medial genicular

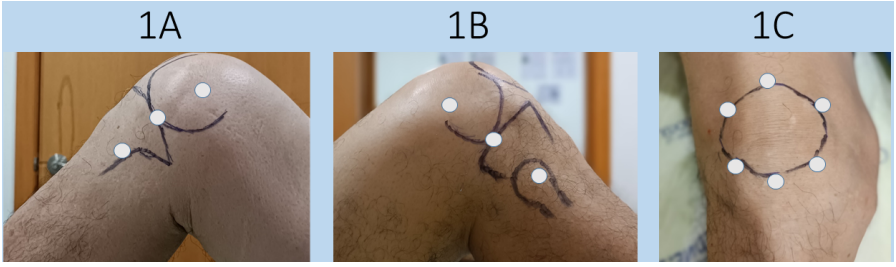

Figure 1. The Biopuncture application scheme in Knee Osteoarthritis. A basic scheme for the application of Biopuncture in individuals with knee osteoarthritis may include 12 subcutaneous points around the knee. This scheme may vary according to the specific needs of each patient. (A) Medial aspect of the knee, (B) Lateral aspect of the knee, (C) Around the patella.

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nerve [10, 61-63]. It coincides with the SP-9 acupuncture point [43]. Here, 2 mL should be applied (Fig. 1A).

4. A point on the most proximal edge of the lateral femoral condyle: This point coincides with the proximal insertion of the lateral collateral ligament, the passage of the iliotibial band, and the emergence of the superior lateral genicular nerve [10, 61-63]. It coincides with the ST-34 acupuncture point [43]. Here, 2 mL should be applied (Fig. 1B).
5. A point at the lateral joint line level: This point coincides with the coronary ligaments of the lateral meniscus [63] and with the passage of branches of the superior lateral genicular nerve [10, 62]. It coincides with the GB-33 acupuncture point. Here, 2 mL should be applied (Fig. 1B).
6. A point on the anterior edge of the fibular head: This point coincides with the distal insertion of the lateral collateral ligament and the emergence of the inferior lateral genicular nerve [10, 61-63]. It coincides with the GB-34 acupuncture point [43]. Here, 2 mL should be applied (Fig. 1B).
7. Three points on the upper edge of the patella (one lateral, one central, and one medial): These points coincide with the insertion of the quadriceps tendon, the suprapatellar bursa, and the passage of branches of the anterior femoral cutaneous nerve [63]. Here, 1 mL should be applied (Fig. 1C).
8. Three points on the lower edge of the patella (one lateral, one central, and one medial): These points coincide with the insertion of the patellar tendon, the infrapatellar bursa, and the passage of the infrapatellar nerve (saphenous branch) [63]. Here, 1 mL should be applied (Fig. 1C).

The above-mentioned areas of the knee are among the most sensitive ones because they have a higher concentration of nociceptors [10, 61, 62]. This scheme can be applied completely or partially, and it should be modified depending on the needs of each patient.

The number of applications recommended is three to six sessions at weekly to biweekly intervals [12, 16].

DISCUSSION

Biopuncture is a therapeutic strategy that can be useful in individuals with KOA. It has the following advantages:

Given the components of the solutions used in biopuncture, it represents a multitarget therapeutic strategy that affects various levels of the pathophysiological process observed in KOA. It integrates mechanisms of action that modulate inflammation and desensitization, in addition to exhibiting antidegenerative and proliferative effects.

Its application through periarticular subcutaneous infiltration is a simple technique with a low risk of complications [64].

Biopuncture can be used with other KOA treatments. Its components have been simultaneously applied to other treatments, such as physiotherapy [65] or oral treatments with NSAIDs [66], slow-acting disease-modifying drugs [67], or even the same antihomotoxic drug, such as Zeel, which may exhibit similar therapeutic efficacy to NSAIDs in controlling pain and improving function in individuals with KOA [68]. It can also be simultaneously applied with intra-articular injections of hyaluronic acid [69], dextrose [70], or ozone [71], which can result in greater efficacy because of the therapeutic effect of biopuncture on periarticular structures.

Biopuncture can also have some disadvantages:

The application of biopuncture in individuals with KOA can cause minor side effects, such as ecchymosis and pain at the point of application, as noted in studies in which the biopuncture components were applied subcutaneously [44, 57].

Although antihomotoxic drugs, such as Traumeel and Zeel, are marketed in many countries [17], they are not available in every country; therefore, their use is not always possible. Fortunately, various companies are manufacturing drugs with equivalent formulas that may be able to replace them [13].

More clinical studies on the use of biopuncture for treating individuals with KOA are warranted to corroborate its efficacy and therapeutic safety and to identify the treatment scheme and substance combination that are most appropriate for the treatment of KOA. Similarly, more studies are needed to establish the therapeutic effect of each substance in the biopuncture mixture. Although some clinical studies have demonstrated the efficacy of antihomotoxic drugs alone in comparison with other therapeutic substances in the treatment of musculoskeletal pain [39, 72], no randomized clinical trial has assessed the effect of the biopuncture mixture in comparison with other therapeutic substances.

CONCLUSIONS

Biopuncture appears to be a potential, simple, and low-risk therapeutic strategy for KOA. It can be applied through periarticular subcutaneous injections. Moreover, it has multitarget

mechanisms of action that can intervene at various physiopathological levels, such as the modulation of the inflammatory process, reduction of peripheral sensitization, and stimulation of antidegenerative and trophic mechanisms in the affected structure. Consequently, it can reduce pain and improve function. Hence, it may be a viable intervention for use in the integrative treatment of individuals with KOA.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this work.

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SUPPLEMENTARY MATERIALS

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