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PERSPECTIVE

Placebo effects in musculoskeletal radiology procedures

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The word placebo translates from Latin as "I will please" and was originally defined in 1811 as "a medicine given more to please than to benefit the patient" [1]. Placebo use was widespread by the early twentieth century, thought to appease patients without affecting pathophysiology [2]. Studies of angina treatments in the 1930s used the word placebo to describe the inert agent given to control groups [3]. Subsequent research acknowledged therapeutic potential of inert agents in controls, such as Beecher's quantification of placebo effect magnitude [4]. Revised definitions included the following by Shapiro in the 1960s: "any therapeutic procedure which has an effect on a patient, symptom, syndrome or disease, but which is objectively without specific activity for the condition being treated" [5]. Nocebo effects are adverse effects or worsening of a condition after placebo administration. We hypothesized that placebo analgesia could account for a proportion of the therapeutic effect of analgesic procedures performed by musculoskeletal radiologists and reviewed the relevant literature.

The complex mechanisms of placebo effect were described by Goffaux in a triphasic model [6]. The first phase, induction, involves conditions that favor placebo effects, such as therapeutic message and alliance, administration method, the patient's beliefs and history, and sociocultural factors. Much of patient expectation is formed from the explanation of a procedure in advance by the practitioner, which can influence the placebo effect [7]. Lack of empathy and negative non-verbal behavior such as lack of eye contact contribute to nocebo effects and lessen placebo effects [8]. The second phase of the model involves psychological variables, including conditioning from previous experience, motivation and desire for relief, and emotional state [6]. An optimistic disposition has been shown to promote focus on recovery and lower pain scores in post-operative patients [9]. The psychological mediators are linked to neurochemical responses: associations have been demonstrated between placebo effects and release of endogenous opioids [10] and endocannabinoids [11]. Following the biological responses, the third phase of actualization involves expression of placebo responses such as subjective changes in pain, emotions, quality of life, and need for additional analgesia and other objective clinical indicators [6].

Placebos are integral to controlled trials, including those involving analgesics. Participants in blinded trials are unsure whether they receive the treatment or placebo; therefore, the placebo effect in such trials is weaker than in clinical practice where the patient may have higher expectation of analgesic effect. A meta-analysis by Vase found a significantly higher placebo mean effect size (0.95) in studies investigating placebo analgesia compared to that in studies using placebo as a control (0.15), suggesting a contribution of conditioning to analgesia [12]. A trial by Pollo [13] administered a saline infusion to post-thoracotomy patients in addition to buprenorphine on request, informing one group of patients that the saline was a potent analgesic, and double-blinding another group who were told that the infusion was either a painkiller or placebo. Compared to controls, both groups showed a reduction in opioid requirements, larger in the group informed that the saline was a painkiller. A 2010 Cochrane Review found that placebo interventions have varied effects on pain, from negligible to clinically important [14]. Meta-regression analyses showed that larger effects of placebo interventions were associated with physical interventions, trials with the explicit purpose of studying placebo, and trials that did not inform patients of possible placebo intervention [14].

Placebo trials in radiology

Randomized controlled trials in interventional techniques are difficult to design as the possibility of sham intervention, required to form an appropriate control group, may not be

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acceptable when explained to potential participants eager for analgesia. True placebo interventions would necessitate injection of an inert agent to an area other than that desired for pain relief, for example outside the epidural space or away from facet joint nerves. However, contribution of placebo effect to pain relief is evident in a number of randomized controlled trials that do not specifically examine placebo analgesia or compare placebo techniques.

Image-guided facet joint complex interventions include diagnostic and therapeutic facet nerve blocks, using local anesthetic to target pain of facet arthropathy transmitted by the medial branches of the dorsal rami. Local anesthetic injection on the medial branch nerve can be expected to relieve pain for its duration of action, but relief lasting longer from anesthetic alone is unlikely. In randomized controlled trials examining medial branch blocks with or without corticosteroid for facet joint pain, Manchikanti reported significant pain relief over 6 to 24 months in at least 82% of patients with lumbar [15] and in at least 85% of patients with cervical facet joint pain [16], regardless of corticosteroid administration. The duration of analgesia reported is substantially longer than expected for local anesthetic alone and can therefore be at least partially attributed to placebo effect. A similar conclusion can be drawn from a trial comparing radiofrequency lumbar facet denervation to sham treatment, which found no differences between the interventions in terms of visual analog scale (VAS), physical activities, and analgesic intake; however, the VAS improved in both groups [17].

An initial conservative approach to discogenic back pain or radiculopathy, with rest and physiotherapy, is the mainstay of treatment. Combined epidural local anesthetic and corticosteroid injections are commonly used as an adjunct, with indications including radiculopathy and spinal stenosis [18]. Transforaminal epidural injections target the epidural space where the nerve root exits the spinal canal and are performed using fluoroscopic or CT guidance. Caudal epidural injections access the epidural space through the sacral hiatus. A randomized trial by Karppinen comparing lumbosacral transforaminal epidural corticosteroid injection to saline injection for radiculopathy in 160 patients found corticosteroid to be more effective than saline at 2 weeks but not more effective than saline at 12 months [19]. Notably, patients receiving saline injection reported significant improvement in back and leg pain at 6 months. Ng compared transforaminal epidural injection of corticosteroid or bupivacaine in 86 patients, finding modest improvement in both groups but no significant differences between groups at 2- to 12-week follow-up [20]. Anderberg compared cervical transforaminal epidural corticosteroid and anesthetic injections to saline and anesthetic injections, finding no significant difference at 3 weeks but a persistent positive response in 30% of patients in both groups [21]. Caudal epidural lidocaine injections with and without corticosteroid were compared in a randomized trial by Manchikanti, finding no significant difference in overall relief between the groups over 2-year follow-up, although average relief per procedure was superior for corticosteroid [22]. Similar to the aforementioned facet nerve block trials by the same author, duration of analgesia reported is longer than expected for local anesthetic and implies some contribution of placebo effect. It is important to note, however, that the findings of these epidural injection trials reflect a typical self-limiting pattern of discogenic or radicular pain, with early increased analgesia in the treatment arm, followed by expected improvement in both the treatment and control groups at 6 months and no difference at 2 years. This may seem to imply placebo effect but the natural history of discogenic pain should be taken into account and, as previously mentioned, an initial conservative approach should be promoted.

The use of vertebroplasty has been credited with substantial improvement in pain related to vertebral fractures. However, two randomized controlled trials comparing vertebroplasty to a sham intervention without cement injection [23] and to conservative treatment [24] inferred that the benefit from vertebroplasty derives from placebo effect. Kallmes randomized patients after sterile preparation and injection of skin and periosteal local anesthetic to polymethylmethacrylate (PMMA) injection or sham procedure. The sham procedure involved verbal and physical cues such as pressure on the patient's back and opening of the methacrylate monomer to simulate the odor of PMMA, but the needle was not placed [24]. Buchbinder employed a similar approach with the control group but included a further step of inserting a 13-gauge needle to rest on the lamina. The central sharp stylet was then replaced with a blunt stylet, and the vertebra was gently tapped to simulate vertebroplasty, along with preparation of PMMA to produce its odor in the room [23]. Both trials concluded that improvements in pain in patients treated with vertebroplasty were similar to improvements in the control groups, and no beneficial effect of vertebroplasty over the sham procedures was observed. Patients in the treatment and control groups in both studies experienced significant pain relief, owing presumably to the treatment ritual and contextual factors.

Outside the realm of spinal intervention, other treatments performed by musculoskeletal radiologists have been subject to randomized controlled trials demonstrating beneficial placebo effects. Heyworth acknowledged prominent placebo effect in injection therapy of the first carpometacarpal joint, having demonstrated significant improvement in VAS scores from baseline to 4 weeks in a placebo group [25]. While showing platelet-rich plasma (PRP) to be more effective than placebo injection in carpal tunnel syndrome, a small randomized trial by Malahias reported improvement in eight patients in a placebo group, possibly due to hydrodissection or true placebo effect [26]. Montalvan demonstrated PRP to be no more effective than placebo in humeral epicondyle injection,

but pain scores significantly decreased in both groups [27]. A pilot randomized trial comparing intra-articular knee injection of corticosteroid and placebo demonstrated significant improvements in VAS in both groups, as well as reduction in synovial hypertrophy which was significant in the treatment group and non-significant in placebo. The authors hypothesize expectancy-induced descending inhibition of pain, reducing local inflammation through activation of the hypothalamic-pituitary-adrenal axis [28].

A single-blind randomized trial by Li investigated the role of music in patient anxiety related to musculoskeletal radiology procedures [29]. Patients were randomized to groups offered and not offered ambient music during their procedure. According to an exit survey, patients in the group offered music had significantly lower post-procedural pain and greater decrease in pain compared to those not offered music. Within the group offered music, there was no significant difference in pain if music was accepted or declined, but there was a non-significant decrease in post-procedural pain in those who listened to music. The authors concluded that the option to control an aspect of the procedure may contribute to analgesia and decreased anxiety, along with reduction of pain-related neural activation following pleasant musical stimuli [30].

Enhancing the placebo effect in musculoskeletal radiology

The musculoskeletal radiologist should be aware that a proportion of therapeutic success is related to placebo effect, as demonstrated by the large effect size in a meta-analysis of placebo analgesia [12]. A positive, confident attitude of both clinician and patient to treatment can increase efficacy. Stating reassurance, such as that the treatment provides relief to the majority of patients, has been shown to produce positive results [6]. Providing overly worrisome information to a patient when obtaining consent is less advisable, particularly in the setting of significant pre-procedure anxiety. Verbal and other sensory cues such as comfort and medical odors could contribute to placebo effect. Patient experience and treatment efficacy can improve if the patient is given control over some aspect of their procedure, such as music played in the procedure room [29].

The findings of the aforementioned placebo trials raise an ethical question. Considering that numerous studies demonstrate little or no difference between treatment and placebo groups, the inherent risks of injected medications such as corticosteroids and local anesthetic could arguably be regarded as outweighing their benefit if sham procedures can produce similar effects. The benefit of placebo could be combined with potentially efficacious inert treatments such as dry needling or saline injection, which may have therapeutic mechanical effects including hydrodissection, mechanical scar tissue disruption, or incitement of local bleeding response. The avoidance of drug injection in favor of inert treatments would require specific discussion with patients to ensure their understanding and confidence in the intervention.

Conclusion

Complex interactions between conditioning, social factors, and neurophysiological processes produce placebo analgesia, which can and should be promoted by musculoskeletal radiologists in the setting of analgesic procedures. Placebo analgesia is greater in clinical practice than in experimental contexts, as the patient likely has higher expectation of analgesic effect. It is essential that practitioners are aware of placebo effect, its influence on analgesia, and how to potentiate it in their own clinical practice.

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