Contemporary Clinical Trials 57 (2017) 51–57

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Optimizing delivery of a behavioral pain intervention in cancer patients using a sequential multiple assignment randomized trial SMART☆

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ARTICLE INFO

Keywords:
Smart
Novel trial designs
Breast cancer
Pain
Pain coping skills training
Symptom management

ABSTRACT

Background/aims: Pain is common in cancer patients and results in lower quality of life, depression, poor physical functioning, financial difficulty, and decreased survival time. Behavioral pain interventions are effective and nonpharmacologic. Traditional randomized controlled trials (RCT) test interventions of fixed time and dose, which poorly represent successive treatment decisions in clinical practice. We utilize a novel approach to conduct a RCT, the sequential multiple assignment randomized trial (SMART) design, to provide comparative evidence of: 1) response to differing initial doses of a pain coping skills training (PCST) intervention and 2) intervention dose sequences adjusted based on patient response. We also examine: 3) participant characteristics moderating intervention responses and 4) cost-effectiveness and practicality.

Methods/design: Breast cancer patients ($N = 327$) having pain (ratings ≥ 5) are recruited and randomly assigned to: 1) PCST-Full or 2) PCST-Brief. PCST-Full consists of 5 PCST sessions. PCST-Brief consists of one 60-min PCST session. Five weeks post-randomization, participants re-rate their pain and are re-randomized, based on intervention response, to receive additional PCST sessions, maintenance calls, or no further intervention. Participants complete measures of pain intensity, interference and catastrophizing.

Conclusions: Novel RCT designs may provide information that can be used to optimize behavioral pain interventions to be adaptive, better meet patients' needs, reduce barriers, and match with clinical practice. This is one of the first trials to use a novel design to evaluate symptom management in cancer patients and in chronic illness; if successful, it could serve as a model for future work with a wide range of chronic illnesses.

1. Introduction

Patients with cancer report pain as their most distressing and feared symptom [1,2]. The incidence of moderate-to-severe pain in cancer patients remains > 50%. Patients with high levels of pain have poor physical functioning, more physical symptoms, higher levels of depression, increased financial difficulty [3,4], and decreased survival time [5]. While analgesics are the primary therapy for cancer-related pain [6], behavioral pain interventions are an efficacious adjuvant therapy [7,8]. Behavioral pain intervention protocols teach patients strategies for managing psychosocial factors that contribute to pain [9]. Randomized clinical trials (RCT) have supported the efficacy of these interventions; meta-analyses report patients experience significant pain reduction in 65–86% of RCTs [7]. NIH guidelines recommend that behavioral interventions be integrated into treatment for cancer patients experiencing pain [10]; however, implementation remains low.

Pain Coping Skills Training (PCST) is a behavioral pain intervention that has demonstrated efficacy for reducing pain [11]. Traditionally,

☆ Grant acknowledgement, source of support: This work is supported by a grant awarded to the senior author TJS from the NIH/NCI 1R01CA202779-01.
Trials registration: ClinicalTrials.gov, NCT02791646, registered 6/2/2016.

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http://dx.doi.org/10.1016/j.cct.2017.04.001
Received 21 December 2016; Received in revised form 21 March 2017; Accepted 8 April 2017
Available online 11 April 2017
1551-7144/

PCST has been delivered to patients having persistent pain in weekly sessions, in a predetermined dosage or set number of hour-long, face-to-face sessions. PCST protocols train patients in multiple cognitive-behavioral skills (e.g., relaxation, imagery, activity pacing) with the goal of enhancing their abilities to manage pain by changing thoughts, feelings, behaviors, and body responses. PCST protocols vary with regard to the numbers of sessions, duration of sessions, and variety of skills taught. Nevertheless, these protocols have shown success in reducing pain, physical and psychological disability, and improving self-efficacy for pain management and quality of life [8,9,12–14].

Traditional RCTs of behavioral pain interventions evaluate outcomes achieved with a "one size fits all" approach in that they test a set intervention time and dose with response assessed post-treatment. This approach poorly matches actual clinical practice where intervention response is assessed in an ongoing fashion, intervention dose and techniques are adapted based on response, and patient characteristics influence intervention choices. There is growing interest in novel RCT designs that can provide information to optimize behavioral pain interventions. The importance of study designs that are adaptive, better meet patients' pain needs, and match approaches used in clinical practice has been recognized. We utilize a novel treatment approach to conduct a controlled clinical trial, the sequential multiple assignment randomized trial (SMART) design. A SMART design is a study design that allows evaluation of adaptive interventions in which the type or dose of treatment is individually tailored based on the patient's needs [15]. The purpose of this paper is to describe the rationale, design, methods and analyses of a novel RCT that aims to inform treatment efficacy and whether an adjustment to the dose of an initial intervention can improve patient response when a significant pain reduction is not achieved.

2. Methods

This study was approved by the Institutional Review Board. Recruitment procedures comply with HIPAA guidelines.

2.1. Study aims

Our *first aim* is to provide comparative evidence of response to differing initial doses of a behavioral pain intervention (i.e., PCST-Full vs. PCST-Brief). Our *second aim* is to provide comparative evidence of intervention dose sequences of PCST, which adjust dose based on patient response. Our *third aim* is to determine participant characteristics that moderate responses to initial and secondary doses of PCST following each dose and at 6-months and to derive an optimal adaptive treatment strategy for personalizing selection of initial and secondary interventions based on patient characteristics. Our *fourth aim* is to evaluate the incremental cost-effectiveness and practicality of alternative intervention dose sequences of PCST.

2.2. Study design

This study uses a SMART design (Fig. 1). Patients with breast cancer (stage I-IIIC; $N = 327$) who have pain are recruited and randomly assigned to either: 1) PCST-Full or 2) PCST-Brief. Patients will be identified from a pain report in their electronic medical records and screened at recruitment to assess a pain intensity rating of ≥ 5 out of 10. Randomization will be 1:1 with equal allocation to each initial intervention; no stratification will be used. Participants randomized to PCST-Full receive 5 weekly sessions in pain coping skills training with a trained therapist. The PCST-Brief condition consists of one 60-min, in-person, PCST session (i.e., rationale for training in pain coping skills, progressive muscle relaxation, imagery). Five to 8 weeks following randomization, participants are asked to rate their pain intensity during the past week; all participants are then re-randomized based on their pain rating. Participants in the PCST-Full arm who respond to the intervention by reporting a > 30% reduction in their pain intensity level are re-randomized to receive either a maintenance dose or no further intervention. Participants who do not respond (< 30% pain reduction) are re-randomized to receive an increased dose or maintenance. Participants in PCST-Brief who report at least a 30% reduction in their pain intensity level are re-randomized to receive either a maintenance dose or no further intervention; participants who do not respond to PCST-Brief are re-randomized to receive an increased dose or a maintenance dose. Upon determining response, secondary randomization will also be 1:1 with equal allocation into one of the two appropriate response sequences. All participants receive an intervention condition that is expected to lead to pain reduction; participants are not provided with information on which condition is hypothesized to lead to greater pain reduction.

As shown in Fig. 2, all participants complete assessments at baseline, pre-secondary randomization, post-treatment, and six-months post-treatment. Assessments include measures of pain intensity, pain interference, and pain catastrophizing. The baseline assessment also includes measures of depression, social support, and physical performance.

Careful attention has been given to minimize study attrition. Our eligibility criteria include only through cancer stage IIIC, which may minimize attrition due to health or death. We have also very carefully trained study staff, including recruiters, coordinators, and therapists, to communicate expectations to participants and to decrease breaks in communication with participants (e.g., at second randomization) to minimize attrition. For example, we've created study "road map" worksheets that are used to aid in discussion with participants. Our study team meets weekly to track each participant's progress in the study. Finally, we send text messages to participants (3 times per week) to remind them to practice skills, but also view this as a strategy to keep participants engaged. Text reminders for appointments are available to participants who indicate they would be helpful.

2.3. Participant eligibility criteria

Eligible participants include patients with a diagnosis of breast cancer (initial or recurrence) within the past two years. Other eligibility criteria are: ≥ 21 years old, a life expectancy of at least 12 months, a pain intensity rating ≥ 5. Exclusion criteria include: cognitive impairment [16], presence of a severe psychiatric condition, or current or past (< 6 months) engagement in PCST for cancer.

2.4. Interventions

2.4.1. Initial randomization

2.4.1.1. Pain coping skills training full (PCST-Full). PCST-Full consists of a 5-session intervention delivered to participants at the medical center by their therapist.

Session 1 – Participants are provided with a brief overview of the session format and given an opportunity to talk about their cancer diagnosis. Participants are then presented with the rationale for training in pain coping skills and the role that thoughts, feelings, behaviors, and body responses can play in the pain experience. This rationale highlights the multidimensional nature of pain through discussions of the gate control theory [17] and neuromatrix [18] theory of pain. Participants are trained in 1) Progressive muscle relaxation (PMR), which involves concentrating on muscle tension signals and using them as cues to relax, and 2) Pleasant imagery, which involves using one's imagination to focus on a pleasant scene using multiple senses to evoke the image (sight, hearing, touch, taste). Relaxation and pleasant imagery are key to start with because they are considered the most widely used and effective pain coping skills [7,8,19–21]. Behavioral rehearsal, modeling, guided practice, and feedback are used to teach both skills. An audio-recording of