Article

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Blinding strategies in the conduct and reporting of a randomized placebo-controlled device trial

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Abstract

Background: Blinding is a fundamental design strengthening feature in randomized clinical trials. Blinding is particularly important in trials whose outcome measures include subjective assessment of signs and symptoms, such as trials investigating the post-thrombotic syndrome, a frequent chronic complication of deep vein thrombosis.

Purpose: To determine whether strategies used to blind site investigators, research coordinators and patients were successful in a specific device trial, a multicenter trial of active versus placebo elastic compression stockings worn for 2 years to prevent post-thrombotic syndrome in patients with a first deep vein thrombosis (the SOX Trial).

Methods: Patients were randomized to the active or placebo stocking intervention, which were indistinguishable in appearance at baseline. Replacement stockings were shipped directly to patients' homes and were not worn to any of the study visits during the study. Guesstimates of treatment group assignment were completed by site investigators, research coordinators and patients at the end of study follow-up. Statistical assessments of blinding were performed using the James and Bang blinding indices.

Results: Overall rates of correct responses were 10.4% for site investigators, 17.8% for research coordinators and 29.4% for patients. James blinding index values suggest that blinding was achieved for site investigators, research coordinators and patients. The treatment specific Bang blinding index values suggest that blinding was achieved for site investigators and research coordinators, but detected possible unblinding and opposite guess for patients in the active and placebo elastic compression stocking groups, respectively.

Limitations: Post-study assessment of blinding, as was done for the SOX Trial, cannot distinguish between degree of blinding and hunches about an intervention's efficacy. However, as rates of post-thrombotic syndrome along with adverse events in the SOX Trial were similar between treatment groups, it is unlikely that hunches would have interfered with our end-of-trial assessment for blinding.

Conclusion: Blinding strategies used in our trial were successful overall and appeared to be most effective for site investigators and research coordinators. For patients, there may have been some degree of unblinding in the active stocking group. However, as the trial results were negative with active elastic compression stocking showing no benefit over placebo elastic compression stocking, this potential unblinding has minimal impact on the overall conclusions of the trial.

Keywords

Blinding, post-thrombotic syndrome, deep vein thrombosis, randomized controlled trial, elastic compression stockings, device trial

Introduction

Blinding is widely accepted as a fundamental methodological component in randomized controlled trials, to help achieve unbiased estimates of treatment effect.[1–4] However, the strategies used to implement, maintain and assess blinding are frequently not well described and at times even overlooked,[5] which makes it difficult to critically appraise the overall quality of study findings.[6–8]

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The post-thrombotic syndrome is a chronic condition which frequently develops after deep vein thrombosis. The post-thrombotic syndrome is characterized by persistent leg symptoms, disability and reduced quality of life, which impose a large burden on patients and society.[9–12] In randomized controlled trials of interventions to prevent the post-thrombotic syndrome, blinding is especially important because a number of subjective signs and symptoms must be assessed to make the diagnosis. Two previous trials have reported that wearing elastic compression stockings for 2 years following a deep vein thrombosis substantially reduced the risk of developing the post-thrombotic syndrome.[13,14] However, patients under investigation and research personnel were not blinded to treatment assignment in these open-label studies. A large, multicenter randomized controlled trial that examined the effectiveness of active versus placebo elastic compression stockings to prevent the post-thrombotic syndrome was conducted in an attempt to overcome the potential limitations of the previous open-label trials (the SOX Trial).[15]

We report here on the unique strategies used to implement, maintain and assess blinding to the study intervention, and their effectiveness, for site investigators, research coordinators and patients who participated in the SOX Trial.

Methods

The design of the SOX Trial is described in detail elsewhere.[15,16] Briefly, patients with a first symptomatic, objectively confirmed proximal vein deep vein thrombosis were eligible to participate in the trial. Randomization to active (30–40 mm Hg pressure at the ankle) or placebo (<5 mm Hg, that is, no active compression) elastic compression stockings was performed centrally and stratified by centre using varying block sizes of 4 and 8. Study visits were performed at baseline (within 2 weeks of deep vein thrombosis diagnosis), 1 and 6 months and then every 6 months until the 24-month follow-up visit. The primary outcome was cumulative incidence of post-thrombotic syndrome from 6 months onwards. Outcomes were measured at every study visit, unless otherwise indicated. Patients were instructed to wear their stocking on the affected leg from waking to retiring for 2 years and were encouraged to stay active during this time.

Blinding procedures

Establishing the blind

As only those patients with a first deep vein thrombosis were eligible for enrolment, participating patients were very unlikely to have previously worn active compression stockings. Active and placebo elastic compression stockings, which were manufactured to be indistinguishable in appearance, were shipped directly from the stockings manufacturer's central distribution centre to patients' homes, within 2 weeks of deep vein thrombosis diagnosis.

Maintaining the blind

To maintain the blind, replacement study stockings were shipped every 6 months from the central stockings facility directly to patients' homes. In addition, patients were instructed not to wear their study stockings to any of their attended study follow-up visits. During site initiations, site investigators and research coordinators were instructed not to ask patients about their stockings or look at or handle stockings if they were accidentally brought to a study visit. Checks were performed quarterly at the central stockings facility to ensure that stockings allocated throughout a patient's participation in the study correctly corresponded to their treatment allocation at randomization.

Assessing the blind

Blinding was assessed by a guesstimate of treatment intervention (i.e. active, placebo or don't know) at the end of study follow-up by asking site investigators, research coordinators and patients 'Which type of stocking do you think patient received during the SOX Trial?' Individuals were also asked to rate the confidence of their guesstimate (i.e. extremely, reasonably or slightly) when an active or placebo response was provided.

Statistical methods

The James and the Bang Blinding indices (BIs) were used to statistically assess success of blinding. The James' index calculates the overall degree of disagreement between the allocated treatment and guesstimate, where BI values of 1, 0.5 and 0 represent blinding, random guessing and unblinding, respectively.[17] The James index can be used to assess overall blinding success, but it does not distinguish between differences between treatment arms. The James index places the highest weight on 'don't know' responses. Hence, there is an implicit assumption that these responses are honest and not simply offered to avoid having to make an actual judgement.

The Bang BI assesses the degree of blinding within each treatment group, where $BI > 0.2$ and $BI < -0.2$ are considered by the developer to represent unblinding and opposite guesstimate, respectively; any value in between is considered to represent successful blinding (i.e. random guesstimate).[18] With the Bang BI, there is less emphasis on 'don't know' responses as greater weight is placed on the identified responses (i.e.

correct/incorrect). The Bang BI also provides an estimate of the proportion of correct responses provided in excess of chance.[3] Analyses were conducted in Stata/IC 11.2 (StataCorp, College Station, TX, USA) using the 'blinding' module written by Jiefeng Chan of Texas A&M University.

Results

Study population

From June 2004 to February 2010, 806 patients at 24 recruiting sites in Canada and the United States, who met eligibility criteria for the SOX Trial and provided informed consent, were randomized to the active and placebo stocking groups. Three ineligible patients were excluded from the analysis; hence, in total, 803 patients were included in the modified intent-to-treat analysis (409 in the active and 394 in the placebo groups). The trial results are described in detail elsewhere.[15] Briefly, active and placebo elastic compression stockings groups were comparable with respect to demographic characteristics and venous thrombosis risk factors at baseline (Table 1). The cumulative incidence of post-thrombotic syndrome was similar in the active and placebo groups (14.2% vs 12.7%; hazard ratio ($HR_{adjusted\ for\ centre}$) = 1.13; 95% confidence interval (CI) = 0.73, 1.76; p = 0.58). Minor adverse events (rash, itching) occurred in eight active elastic compression stockings and seven placebo elastic compression stockings patients; there were no serious adverse events that were attributed to the study intervention in either group. Study stocking use was similar between groups, as was the use of other co-interventions (e.g. anticoagulants, anti-inflammatory medication). During the study, 33 patients in the active elastic compression stockings group withdrew from the study, and 23 were lost to follow-up, similar to 37 and 21 patients, respectively, in the placebo elastic compression stockings group. Attendance at the study visits was similar between groups.

Blinding assessments

Most site investigators, research coordinators and patients (93.8%, 96.4% and 84.8%, respectively) provided responses to the assessment of blinding questions at the end of study follow-up. For the three categories of responders, the majority reported 'don't know'. Overall rates for correct guesstimates were 10.4% for site investigators, 17.8% for research coordinators and 29.4% for patients. Results for guesstimate of treatment group for the two interventions are presented in Table 2. The proportion with correct responses of treatment assignment for the active elastic compression stockings intervention were 12.6% for site investigators, 23.9% for research coordinators and 41.4% for patients; the proportion for the placebo elastic compression stockings intervention were 8.1% for site investigators, 11.6% for research coordinators and 17.0% for patients.

Overall, correct guesses were provided for 78.9% reporting that they were extremely confident, 62.7% reporting they were reasonably confident and 55.4% reporting they were slightly confident. This trend was also noted for the site investigator, research coordinator and patient sub-groups as well.

Blinding success was also assessed by computing two statistical indices. For the James' index where values > 0.5 suggest adequate blinding, values were 0.90 (95% CI = 0.88–0.91) for site investigators, 0.82 (95% CI = 0.80–0.85) for research coordinators and 0.71 (95% CI = 0.68–0.73) for patients, suggesting that blinding was achieved. For the Bang index where values between -0.2 and 0.2 indicate successful blinding, values for the active and placebo elastic compression stockings groups

Table 1. Baseline characteristics of SOX Trial participants.

	Study group, n (%)[a]	
	Active Stockings (N = 409)	Placebo Stockings (N = 394)
Baseline characteristics		
Age, mean (SD), years	55.4 (15.3)	54.8 (15.8)
Male	255 (62.4)	228 (57.9)
Caucasian	371 (90.7)	354 (89.9)
Body mass index, mean (SD), kg/m^2	29.0 (6.1)	28.9 (6.1)
Outpatients	355 (86.8)	344 (87.3)
DVT risk factors		
Surgery, last 3 months	77 (18.8)	64 (16.2)
Trauma, last 3 months	42 (10.3)	51 (12.9)
Immobilized in last month	67 (16.4)	61 (15.5)
Active cancer[b]	52 (12.7)	46 (11.7)

SD: standard deviation; DVT: deep vein thrombosis.
[a]Unless otherwise indicated.
[b]Diagnosed within last 6 months or treatment ongoing or metastatic or palliative.

Table 2. Guesstimate versus treatment assignment.

Treatment assignment	Site investigators (n = 753)		Research coordinators (n = 774)		Patients (n = 681)	
	Active stockings	Placebo stockings	Active stockings	Placebo stockings	Active stockings	Placebo stockings
Guesstimate[a]						
Active	48 (12.6)	22 (5.9)	94 (23.9)	52 (13.7)	143 (41.4)	104 (31.0)
Placebo	4 (1.0)	30 (8.1)	11 (2.8)	44 (11.6)	14 (4.1)	57 (17.0)
Don't know	330 (86.4)	319 (86.0)	289 (73.4)	284 (74.7)	188 (54.5)	175 (52.1)
Degree of confidence in response[a]						
Correct guesstimate						
Extremely confident	18 (40.9)	11 (40.7)	15 (16.9)	10 (23.8)	66 (48.2)	18 (34.0)
Reasonably confident	21 (47.7)	10 (37.0)	66 (74.2)	22 (52.4)	64 (46.7)	25 (47.2)
Slightly confident	5 (11.4)	6 (22.2)	8 (9.0)	10 (23.8)	7 (5.1)	10 (18.9)
Missing	4	3	5	2	6	4
Incorrect guesstimate						
Extremely confident	0 (0.0)	4 (21.1)	2 (18.2)	3 (6.1)	2 (14.3)	26 (25.7)
Reasonably confident	1 (25.0)	11 (57.9)	6 (54.5)	36 (73.5)	7 (50.0)	63 (62.4)
Slightly confident	3 (75.0)	4 (21.1)	3 (27.3)	10 (20.4)	5 (35.7)	12 (11.9)
Missing	0	3	0	3	0	3
Blinding indices						
James' Blinding Index[b]	0.90 (0.88, 0.91)		0.82 (0.80, 0.85)		0.71 (0.68, 0.73)	
Bang Blinding Index[b]						
Active Stockings	0.12 (0.09, 0.14)		0.21 (0.17, 0.25)		0.37 (0.32, 0.42)	
Placebo Stockings	0.02 (−0.01, 0.05)		−0.02 (−0.06, 0.02)		−0.14 (−0.20,−0.08)	

James' Blinding Index (BI) assesses overall degree of disagreement between treatment allocation and guess, where a BI < 0.5 represents unblinding. Bang Blinding Index assesses the degree of disagreement in each treatment group, where a BI > 0.2 represents unblinding and a BI < -0.2 represents Opposite Guess or 'Wishful thinking'.

[a]Parentheses denote percentages.

[b]Parentheses denote 95% confidence interval.

were 0.12 (95% CI = 0.09–0.14) and 0.02 (95% CI = −0.01 to 0.05), respectively, for site investigators indicating blinding success. For research coordinators, the Bang index values were 0.21 (95% CI = 0.17–0.25) for the active elastic compression stockings group which suggests a tendency for possible unblinding and −0.02 (95% CI = −0.06 to 0.02) for the placebo group, which suggests blinding success. For patients, the Bang index values were 0.37 (95% CI = 0.32–0.42) for the active elastic compression stockings group, which suggests possible unblinding, and −0.14 (95% CI = −0.20 to −0.08) for the placebo elastic compression stockings group, which suggest a tendency for opposite guesstimate (e.g. 'wishful thinking').[19]

Discussion

In many circumstances, effective blinding can be difficult to accomplish. Our results demonstrate that successful blinding is achievable and measurable in a randomized placebo-controlled device trial; the blinding strategies used in the SOX Trial were successful overall, with the highest success of blinding for site investigators followed by research coordinators and then patients.

The finding that site investigators most frequently provided incorrect guesstimates may have been anticipated since site investigators interacted with patients less frequently than the research coordinators, who saw the trial participants at regular study visits. Nonetheless, achieving the blind in site investigators was very important as they made the final assessment of whether or not a patient had developed post-thrombotic syndrome, the primary study outcome. Furthermore, successful blinding of site investigators throughout follow-up meant that they were less likely to differentially administer co-interventions, withdraw patients or encourage or discourage patients from continuing in the trial.[6] While the site investigators performed the roles of both outcome assessor and care provider for patients participating in the trial, we do not view this as a critical weakness, as diagnosis of post-thrombotic syndrome, the study outcome, was based on standardized criteria and the site investigators received training on performing the post-thrombotic syndrome assessment.

Research coordinators had direct contact with SOX Trial patients at every study visit; hence, there was a greater chance for possible unblinding than with site investigators. Since research coordinators were involved in assessing patients for post-thrombotic syndrome, achieving blinding of research coordinators was important to reduce the likelihood of ascertainment bias in the assessment of study outcomes.[6] Our results suggest

that blinding may have been less than perfect for research coordinators, as the percentage who correctly guesstimated treatment assignment was higher than for the site investigators (17.8% vs 10.4%, respectively), and the Bang BI point estimate for the active intervention was marginally above 0.2, the cut-off for blinding. However, the James BI result is consistent with successful blinding of research coordinators. Since the two BIs offer differing messages with respect to blinding of research coordinators, results need to be interpreted with caution. Overall, however, we feel that a slight tendency for possible unblinding of research coordinators with respect to the active treatment group was unlikely to lead to important ascertainment bias as it was the site investigators who were required to make the final confirmation regarding the presence or absence of post-thrombotic syndrome.

Patients tended to correctly identify treatment more often than site investigators and research coordinators. For the active elastic compression stockings group, the percent of unblinding beyond chance was 37% (95% CI = 32%–42%). While results for the James BI indicate adequate blinding, Bang BI results suggest that both treatment groups were more likely to report receiving the active treatment, which for the active elastic compression stockings group could indicate possible unblinding. Despite our best efforts to implement and maintain the blind during the study, we cannot discount the possibility that patients may have perceived the compressive effects of their stocking or have been exposed to active stockings by friends or family members before or during the trial. Still, these results do not necessarily indicate that our patient-directed blinding strategies were ineffective. During recovery from a deep vein thrombosis, leg symptoms such as pain and swelling and quality of life tend to improve as the patient returns to normal health,[20] a pattern also seen in the SOX Trial.[15] Hence, it is possible that more patients in both groups thought that they had been allocated active stockings simply because they attributed those health improvements to receiving the active study intervention. The similar degree of confidence (i.e. extremely and reasonably confident) expressed by patients who received active and placebo stockings further reinforces our theory that the active and placebo stockings were perceived similarly between the two treatment groups.

A potential limitation of our trial is that blinding was only measured once, at the end of study follow-up. Evaluating success of blinding earlier in the trial is considered by some to be preferable, as post-study assessment cannot distinguish between blinding and hunches about efficacy, nor the expected side effects related to the study intervention.[21] Even so, assessment of blinding earlier in a study is also limited as it does not evaluate whether initial blinding is maintained during the trial.[4]

To our knowledge, our trial is the first to evaluate the effectiveness of elastic compression stockings to prevent post-thrombotic syndrome using a placebo stocking comparator to achieve blinding. Undoubtedly, there is still uncertainty about how best to assess blinding including when to collect blinding-related data;[4] work is needed on how to improve blinding in general as well as in specific settings and contexts. In our trial, we instituted a number of measures during randomization and follow-up to improve our blind. Furthermore, we assessed the success of blinding among site investigators, research coordinators and patients, which is often overlooked when reporting results of blinded randomized controlled trials. As noted, post-study assessments of blinding may be affected by hunches about efficacy. However, in the context of our trial, it is unlikely that hunches would have been a major contaminating factor in our end-of-study blinding assessments as rates of post-thrombotic syndrome along with adverse events were similar between treatment groups. Since studies are performed to address uncertainty about whether or not meaningful differences in efficacy and safety exist between treatment arms, failing to ask about post-study assessments of blinding because there is concern that the treatment efficacy may potentially affect blinding assessments, seems ill-advised. Although still an area in which methodological improvement is needed, an attempt can be made to better deal with the problem of confounding by treatment efficacy, by directly asking trial participants the reasons for their treatment assessment, rather than retreating to the more extreme position of assuming that a trial has been effectively blinded because investigators claim they designed the trial to do that or worse, merely describe the trial as 'blinded'.

As in this and any other 'blinded' trial, examining the effect of the blinding processes plays a crucial role in the interpretation of the study findings and placing them in context. There is an important message to note in the fact that the results from our blinded trial[15] showed no effect of compression stocking to prevent post-thrombotic syndrome in contrast to the conclusion reached in the previous unblinded trials.[13,14] By taking a more rigorous approach with blinding strategies in this study, we feel that we were able to deliver on our promise of addressing the issue of stocking use for post-thrombotic syndrome prevention, in the context of a properly blinded trial.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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