Trajectory of Phantom Limb Pain Relief using Mirror Therapy

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CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with financial interest or nonfinancial interest in the subject matter discussed in this manuscript.

ABSTRACT

Objective: Previous research indicates that mirror therapy reduces phantom limb pain (PLP). Specific aspects of pain relief, namely when it occurs and what symptoms of PLP respond to treatment, have yet to be elucidated. We sought to examine at what time mirror therapy works in those who respond to treatment, the relevance of baseline PLP to when pain relief occurs, and what pain symptoms respond to mirror therapy.

Methods: Data from two independent cohorts of individuals with unilateral lower limb amputation were analyzed for this study (n=33). For both cohorts, mirror therapy consisted of fifteen-minute sessions in which amputees performed synchronous movements of the phantom and intact legs/feet. PLP was measured using a 100-mm visual analogue scale (VAS) and the Short-Form McGill Pain questionnaire.

Results: The severity of PLP experienced at the beginning of treatment affected when pain relief occurred. Those with low baseline PLP experienced a reduction in PLP by session 7 of treatment ($p<.05$), those with medium baseline PLP experienced pain relief by session 14 of treatment ($p<.05$), and those with high baseline PLP experienced pain relief by session 21 of treatment ($p<.05$). Moreover, the typical trajectory of pain relief differed across these three groups. Mirror therapy reduced the pain quality of cramping in addition to several others.

Interpretation: The degree of PLP at baseline affects the time to pain relief using mirror therapy. The finding that multiple pain symptoms respond to mirror therapy indicates that the mechanism of action of mirror therapy is not limited to reversing phantom limb paralysis after amputation.

INTRODUCTION

Since its initial documentation nearly 500 years ago (Ambroise Pare), phantom limb pain (PLP)—pain in a missing limb—has eluded effective treatment. Theories of why phantom limb pain occurs include the theory of learned paralysis, the neuromatrix, dissociation between visual and proprioceptive feedback to the brain, and proprioceptive memory. Numerous pharmacologic therapies have failed to reduce pain effectively in randomized clinical trials[1]. One exception is mirror therapy, which appears to be effective and without the side effects that typically accompany pharmaceuticals.

Ramachandran and Rogers-Ramachandran first described mirror therapy over twenty years ago[2]. The therapy stemmed from a theory of 'learned paralysis'[3]. According to this postulate, after amputation the brain still transmits efferent motor commands to the limb, yet, because the limb is missing, it fails to receive afferent sensory signals confirming that the limb successfully moved. As such, the brain perceives the limb as paralyzed, and this illusion of paralysis, in turn, causes pain. Mirror therapy seeks to reverse this paralysis by giving the illusion that the limb responds to motor commands. In mirror therapy, a mirror is placed between the intact and amputated limb to generate the illusion of two healthy limbs. The individual then attempts to move both limbs in synchrony while watching the reflection of the intact limb, thus creating visual feedback that the limb is moving in response to motor commands, which is speculated to reverse the "learned paralysis" that occurs after amputation[2,3]. In their case series, Ramachandran and Rogers-Ramachandran reported that mirror therapy created the illusion of successful movement of the missing limb in six of ten individuals, which for some reduced pain[2]. Subsequent research further supports the efficacy of mirror therapy. A randomized, sham-controlled trial of 22 patients showed that mirror therapy reduced PLP after lower extremity amputation as compared to a covered mirror condition (performing movements in front of a mirror covered by opaque sheet) and mental visualization (imagining movements with the amputated limb)[4]. Furthermore, with the exception of two cases of brief emotional reactions in the mirror group upon seeing the reflected limb, the trial did not detect any adverse side effects to treatment.

In spite of this evidence for the efficacy and safety of mirror therapy, in a survey of over 200 individuals with amputation(s) only 34% had tried mirror therapy; of these individuals, only 40% reported benefit (unpublished data). One potential reason for why research on mirror therapy has yet to translate widely into clinical practice is that the parameters for mirror therapy remain unclear. That is to say, there is no standard treatment protocol for mirror therapy. Moreover, it is unclear who will respond to treatment and how long it takes to see therapeutic benefit. The present paper seeks to

elucidate the treatment parameters of mirror therapy with the hopes of allowing this therapy to enter standard clinical practice. The key items of interest were the trajectory of pain relief using mirror therapy, time to pain relief, the relevance of baseline pain to treatment response, and what pain qualities (e.g., throbbing, cramping, shooting) respond to mirror therapy.

SUBJECTS/MATERIALS AND METHODS

Participants

Data from two independent cohorts with unilateral lower limb amputation were analyzed for this study. In one cohort, participants were recruited from Walter Reed Army Medical Center, Washington, DC. Inclusion criteria included the presence of phantom limb pain greater than 3/10 on a visual analogue scale at least 3 times a week; exclusion criteria included bilateral lower or bilateral upper limb amputation, known neurological disease or brain damage, history of vertebral disk disease/condition, sciatica, or radiculopathy, known uncontrolled systemic disease, concurrent participation in another investigational drug or study device for phantom limb pain or participation in the 30 days immediately prior to study enrollment , current Axis I or II diagnosis determined by a neurologist or psychiatrist in the 6 months prior to entry into the study. The results of this study cohort were previously published and the specific data used for these analyses come only from mirror therapy sessions from the participants[3].

In the second cohort, participants were recruited from Walter Reed Army Medical Center and Walter Reed National Military Medical Center, Bethesda, MD as well as from the community for a functional magnetic resonance imaging study examining the effects of mirror therapy on brain activation patterns. Inclusion criteria included the presence of phantom limb pain greater than 3/10 on a visual analogue scale at least 3 times a week; exclusion criteria included multiple limb amputation, cause of amputation being diabetes or vascular claudication, pending revision surgeries, presence of embedded metallic shrapnel or other metal not compatible with MRI scanning, presence of traumatic brain injury, known neurological disease or brain damage, or history of vertebral disk disease/condition, sciatica, or radiculopathy, known uncontrolled systemic disease, concurrent participation in another investigational drug or study device for phantom limb pain or participation in the 30 days immediately prior to study enrollment, current Axis I or II diagnosis determined by a neurologist or psychiatrist in the 6 months prior to entry into the study, and pregnancy. The results of this study have not yet been published.

Treatment

For both cohorts standard mirror therapy consisted of approximately four weeks of therapy sessions for five days a week, although treatment length and number of days/week varied depending on scheduling. Therapy sessions consisted of three different exercises, each lasting five minutes to total fifteen minutes of therapy per day. Subjects flexed and extended the ankle ("as if stepping on the gas pedal of a car"), moved the foot from side to side ("windshield wiper"), and rotated the foot in a circle ("as if drawing a circle with your toes"), and for those with above knee amputation, flexion and extension of the leg at the knee (additional 5 minutes). At the beginning of each therapy session subjects were instructed to move the intact limb slowly in order that the phantom limb could move at the same pace. In addition subjects were instructed to move the phantom only as much as they could if range of movement was limited and to gradually increase the range of movements with each treatment session. Treatment was either conducted independently (participants followed instructions on their own) or directly observed by an investigator.

Outcome Measures

Visual Analogue Scale

The visual analogue scale (VAS) is widely used in both clinical and research settings to measure pain. The VAS has been shown to be reliable[5], internally consistent[5], and sensitive to treatment[6]. The VAS in both studies consisted of a 100-millimeter horizontal line with two endpoints which were labeled "no pain" (far left) and "worst pain someone could ever experience" (far right). Subjects were instructed to bisect the line at the point that represented their level of PLP over the past 24 hours before each treatment session.

Short-form McGill Pain Questionnaire

The Short-Form McGill Pain questionnaire consists of 15 pain descriptors rated on a scale from 0 (corresponding to none) to 3 (corresponding to severe). The Short-Form McGill Pain questionnaire has been shown to produce similar scores as the standard McGill Pain Questionnaire and be sensitive to treatment[7].

Effective versus ineffective treatment

Mirror therapy was deemed effective versus ineffective depending upon the decline in pain as measured by the VAS. For those with high (> 60 millimeters on the VAS) or medium (31 to 60 millimeters on the VAS) PLP at baseline,

effective treatment was defined as a decline of at least 20 millimeters. For those with low (< 30 millimeters on the VAS) PLP at baseline, effective treatment was defined as a decrease of 50% over the course of treatment.

Participants

Demographics are presented in Table 1. The participants for this study were predominately male (87.5%). The mean age for all study participants was 33 years and the mean time since amputation was 1.8 years.

Analyses

Trajectory of pain relief with mirror therapy

The average pain trajectory across all patients was analyzed using polynomial regression of VAS scores versus treatment sessions. A logit transformation was used to fit the data given the lower limit of 0. Only participants for whom mirror therapy was effective (see definition under the section 'Effective versus ineffective treatment') were included in this analysis, as the question of interest is the time to first noted efficacy of mirror therapy when it works. In addition, a one-way ANOVA was conducted comparing the initial pain level to pain levels on sessions 2, 3, 4, and 5 of treatment to determine whether there is a PLP increase when beginning treatment. This was examined as anecdotally some patients have complained of increased PLP after starting mirror therapy.

Relevance of baseline pain level to treatment response

Data was divided into 3 categories according to baseline phantom limb pain as measured by the VAS: low (VAS score under 30 millimeters), medium (VAS score from 31-60 millimeters), and high (VAS score over 60 millimeters). A polynomial regression of VAS or McGill scores versus treatment sessions was used to look at the trajectory of pain relief for those with effective treatment (see definition under the section Effective versus ineffective treatment). A logit transformation was used to fit the data given the lower limit of 0 for both scales.

Time to pain relief

The data for effective treatment was then analyzed using a one-way ANOVA looking at sessions 1, 7, 14, and 21. These time points were chosen as the trajectory of pain relief indicated these to be the inflection points in treatment

response. A Dunnett multiple comparisons test was used to compare pain levels on session 1 to pain levels on session 7, 14, and 21. We conducted independent analyses for each category of baseline pain (high, medium, and low).

What pain qualities respond to mirror therapy?

The different pain qualities measured by the McGill questionnaire were examined individually to evaluate their specific responses to treatment. The average responses were analyzed using a quadratic regression. All subject data (i.e., those for whom mirror therapy was effective and those for whom it was ineffective) were included in this analysis.

RESULTS

Trajectory of pain relief with mirror therapy

In this combined cohort, mirror therapy was deemed effective for 27 of 31 (87%) subjects. The polynomial regression of VAS versus treatment sessions in these subjects showed a statistically significant decrease in pain over time ($p < .0001$). To allow for the bounded nature of the VAS scale, i.e. there is a lower limit of 0, a logit transformation was used to properly fit the data. As seen in Figure 1, the average pain level of the group decreases substantially over the first 7 treatment sessions, plateaus from sessions 7 to 14, then again declines from session 14 onward. There was no statistically significant increase in pain upon commencement of treatment. A one-way ANOVA with Dunnet's comparisons comparing the initial pain level to treatment 2, 3, 4 and 5 showed no significant difference ($p = 0.761$).

Relevance of baseline pain level to treatment response

To obtain a more quantitative assessment of the pain trajectories, a one-way ANOVA with Dunnet's comparisons was used to compare the difference of the initial treatment pain levels to treatment sessions 7, 14, and 21. The polynomial regression of VAS versus treatment sessions indicated three different trajectories of pain relief for the categories of baseline phantom limb pain severities of low (VAS score under 30), medium (VAS score from 30-60), and high (VAS score over 60).

The low initial VAS sub-group showed an initial decrease in pain through session 7, then a leveling off through session 15 followed by a final decline (see Figure 2A). The medium initial VAS group showed a continuous decrease (see Figure 2B). The high initial VAS group resembled the low VAS group, where there was an initial improvement, a leveling off and then a final improvement (see Figure 2C). Inspection of the individual patient trajectories showed that some of

these patients improved rapidly, while others had an induction period of up to 15 sessions before therapy was effective. Consequently, the initial drop in the aggregate trajectory is related to those patients who improved immediately, while the final drop is from those who maintained high levels of pain through session 15.

Time to pain relief

The Dunnett comparisons showed different findings for the low, medium, and high baseline pain groups. The low baseline pain group showed a significant difference in pain from sessions 1 to 7 (n=8 distinct data measurements), sessions 1 to 14 (n=6 distinct data measurements), and sessions 1 to 21 (n=4 distinct data measurements; see Figure 3A). That is to say, for those with low initial PLP severity for whom treatment was effective, pain significantly dropped by session 7 of treatment. The medium baseline pain group showed a significant difference in pain from sessions 1 to 14 (n=5 distinct data measurements) and sessions 1 to 21 (n=4 distinct data measurements), but not from sessions 1 to 7 (n=7 distinct data measurements; See Figure 3B). This indicates that for those with medium initial PLP for whom treatment was effective, pain significantly dropped by session 14 of treatment. The high baseline pain group showed a significant difference in pain from sessions 1 to 21 (n=3 distinct data measurements), but not from sessions 1 to 7 (n=7 distinct data measurements) or sessions 1 to 14 (n=6 distinct data measurements; See Figure **3C**). For those for with high initial PLP for whom treatment was effective, pain significantly dropped by session 21 of treatment.

What pain qualities respond to mirror therapy?

The quadratic regression looking at the responses of different pain qualities to treatment showed that some qualities showed a significant effect of treatment while others did not. Endorsement of the pain descriptors of throbbing, shooting, stabbing, sharp, cramping, aching, tender, splitting, tiring/exhausting, and punishing-cruel significantly decreased over the course of treatment ($p<.05$), whereas endorsement of the descriptors gnawing, hot/burning, heavy, sickening, fearful did not (Table 2).

Sensitivity analysis

To evaluate the potential bias introduced by attrition, a sensitivity analysis was performed treating the VAS response for all subjects as observations in an intention to treat (ITT) model with a last observation carried forward (LOCF) approach to account for patients who did not complete all planned treatment sessions. This analysis showed minor

differences in the model, and no differences in the overall conclusions. Similarly, a sensitivity analysis of the response from patients with effective treatment showed no deleterious data effects from attrition.

DISCUSSION

This paper is the first to closely examine mirror therapy to determine when, after initiating treatment, an effect is seen and what pain sub-types this treatment works for. The first major finding is that PLP tends to decline rapidly during the first week of mirror therapy, plateau from sessions 7 to 14, and then declines from session 14 onward. However, this trajectory is influenced by the severity of PLP experienced at baseline. Those with low levels of PLP at the onset of treatment show an initial drop through session 7 then a leveling off through session 15 followed by a final decrease. Those with medium levels of PLP at the beginning of treatment show a continuous decline. There appears to be a dichotomy in the trajectory of pain relief for those initiating treatment with high levels of PLP. Some improve rapidly while others experience what appears to be an induction period of up to 15 sessions before a therapeutic effect is seen. Second, pain dropped by session 7 of treatment for those with low levels of PLP ($p<.05$), by session 14 for those with medium levels of PLP ($p<.05$), and by session 21 for those with high levels of PLP ($p<.05$). Finally, the study examined whether mirror therapy reduced certain pain qualities more than others, demonstrating that the pain qualities of throbbing, shooting, stabbing, sharp, cramping, aching, tender, splitting, tiring/exhausting, and punishing-cruel significantly ($p<.05$) decreased over treatment, whereas endorsement of the descriptors gnawing, hot/burning, heavy, sickening, and fearful did not.

Selecting a treatment for PLP can be difficult given the number of treatment options available and how differently persons with major limb amputations can respond to the same treatment[1]. As such, determining early indicators of whether a therapy will work has the potential to tailor treatment to provide pain relief as quickly as possible or to avoid abandoning treatment before a point of efficacy can be expected[1]. Mirror therapy appears to be a treatment that has a high efficacy rate combined with low cost and minimal side effects compared to other treatments for PLP. However, as mirror therapy is not universally effective, it is important to recognize as soon as possible if it will ultimately prove ineffective for an individual, so that the healthcare provider can identify an alternate treatment. Our findings demonstrate that initial PLP severity affects how quickly mirror therapy can lead to pain reduction and may explain why some studies, which had only a single mirror treatment session, did not report the same success rates reported by Chan et al.[4]. Most importantly, some patients with higher initial levels of PLP may take longer to respond to treatment than those with lower pain severity. Although

anecdotally some of our patients reported transient increases in PLP after starting mirror therapy, upon detailed analysis we failed to find a statistically significant increase.

This study also examined how different pain qualities responded to mirror therapy. This analysis is important in that it questions the theoretical underpinnings of mirror therapy. Mirror therapy was developed in response to a postulated theory of 'learned paralysis', in which phantom pain occurs due to the brain "learning" that the missing limb is paralyzed secondary to a mismatch between efferent motor commands and afferent sensory signals after amputation [2,3]. However, there is no evidence that the sensation of cramping, which could correspond to learned paralysis, responds differently to treatment than other pain qualities, such as shooting, which seem not to be connected to paralysis. As such a new theory, or a revision to the original theory, is necessary to account for why mirror therapy works. One possibility is that mirror therapy overwrites proprioceptive memories of the amputated limb as proposed by Anderson-Barnes et al.[15]

Further research is necessary to substantiate and extend these findings. The first cohort was followed for up to 4 months per protocol after treatment ended although some study volunteers were seen incidentally up to 2 years later during routine longitudinal clinical evaluations. For those participants whose PLP had decreased after 1 month of mirror therapy, all except 2 subjects reported that their PLP had resolved. The other 2 subjects reported that their PLP had returned following 2 months and that they had again used mirror therapy for 4 weeks with permanent resolution of PLP thereafter. Much longer follow-up is necessary to determine the long-term efficacy of mirror therapy, as well as the long-term efficacy of most other treatments for PLP. Together, examining predictors of treatment response and the mechanism of action of mirror therapy could contribute to developing a revised mechanism-based classification of PLP[1].

This study has several potential limitations. First, this is a post-hoc analysis of a combined data set which constitutes a larger sample size than originally reported by Chan et al.[4] Second, some participants did not complete the anticipated total number of 20 treatment sessions which could limit statistical power. However, the sensitivity analysis indicates that attrition did not bias study results. Third, since treatment was 5 days per week, data were analyzed by treatment sessions rather than day-to-day changes. Lastly, to fully evaluate the utility of mirror therapy for treating PLP, a prospective comparison of this treatment with other treatments is necessary.

To conclude, this study is the first to examine mirror therapy in terms of when a treatment effect is seen and what pain qualities it treats. Results suggest that the majority of pain relief tends to occur over the first seven sessions of

treatment, although initial PLP severity affects how quickly the response is seen, which has important practical implications for personalized treatment implementation. Additional research is necessary to confirm the importance of baseline pain levels and other characteristics as predictors of treatment response and to identify the mechanism of action of mirror therapy.

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TABLES

Table 1. Demographics

ID	Age	Gender	Site of Amputation	Time since amputation (Years)
C101	21	M	Left Transfemoral	.3
C102	25	M	Right transtibial	1
C103	34	M	Left transtibial	.2
C104	33	M	Left transfemoral	.1
C105	20	M	Right transfemoral	.2
C106	20	M	Right transtibial	.1
C107	25	M	Right transtibial	1
C108	38	M	Left transtibial	.4
C109	23	M	Left transtibial	.1
C110	19	M	Left transtibial	.1
C111	21	M	Left transtibial	.1
C112	31	M	Right transfemoral	.05
C113	39	M	Left transfemoral	1.7
C114	31	M	Left transtibial	.1
C115	22	M	Right transtibial	.2
C116	53	M	Right transfemoral	.2
C117	20	M	Right transfemoral	1
C118	22	M	Right transtibial	.1
C119	30	M	Left transfemoral	.2
C120	29	M	Left transfemoral	.1

C121	20	M	Right transfemoral	.2
C201	59	F	Left transtibial	
C202	21	M	Left transtibial	
C203	52	M	Left transfemoral	2
C204	47	M	Right transtibial	21
C205	75	F	Right transfemoral	5
C206	36	F	Left transfemoral	.25
C207	60	M	Right transfemoral	15
C208	45	F	Right transtibial	1
C209	39	M	Right transfemoral	.5
C210	30	M	Right knee disarticulation	1

Table 2. Reduction in pain in each of the McGill pain characteristics

Pain quality	p value for quadratic regression
throbbing	< 0.001*
shooting	< 0.001*
stabbing	.0053*
sharp	< 0.001*
cramping	.002*
gnawing	.0851
hot/burning	.4226
aching	.0342*
heavy	.5186
tender	.0004*
splitting	.0053*

tiring/exhausting	.0192*
sickening	0.7701
fearful	.0626
punishing-cruel	0.0426*

*p< .05 is considered significant at the 95% confidence level

FIGURE LEGENDS (8 total)

Figure 1. Model of phantom limb pain as measured by the VAS over time

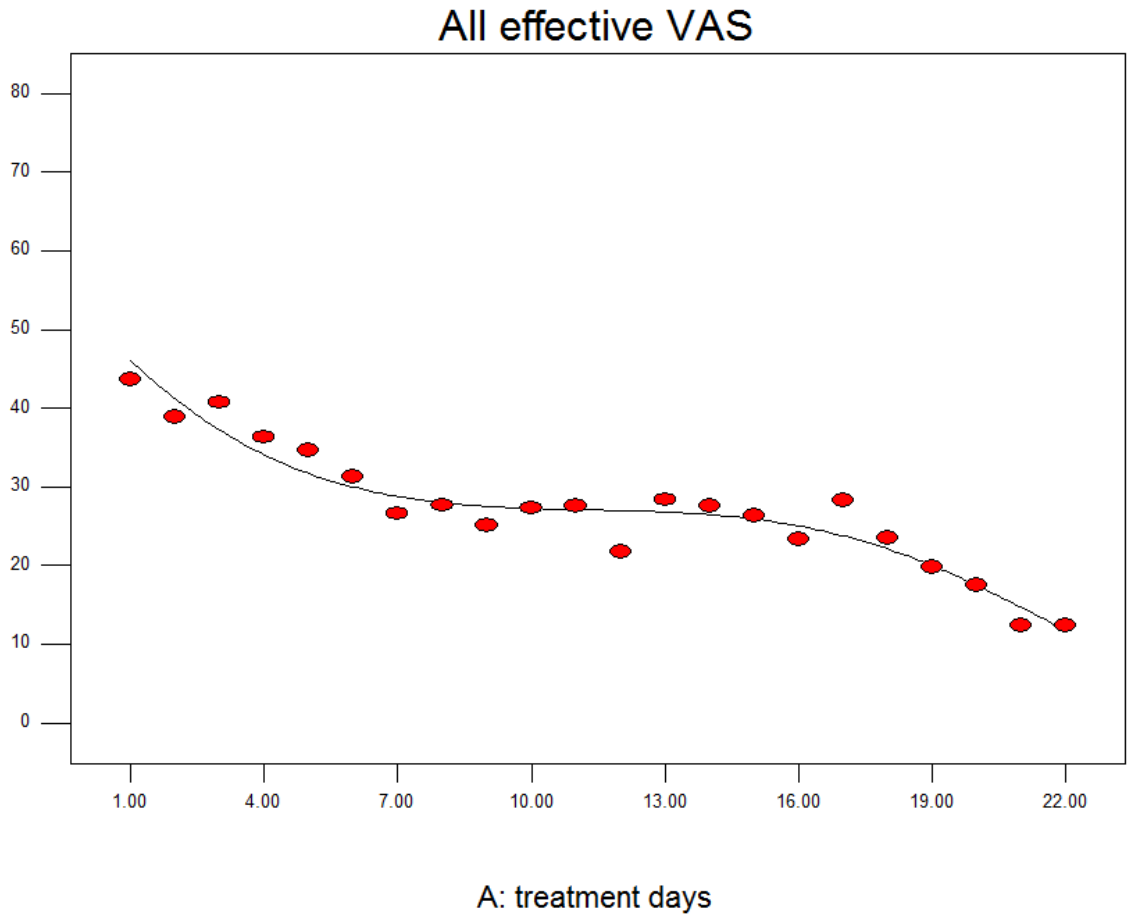


Figure 2. Trajectory of pain relief in those with low initial pain levels

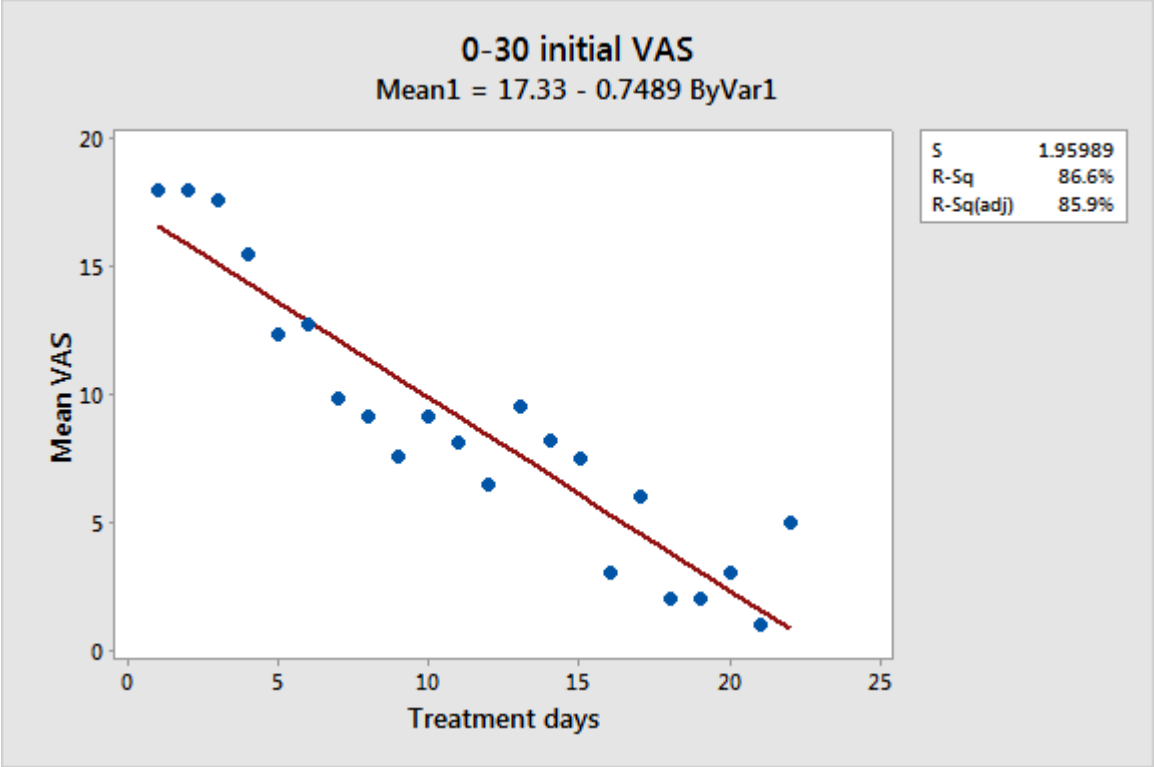


Figure 3. Trajectory of pain relief in those with medium initial pain levels

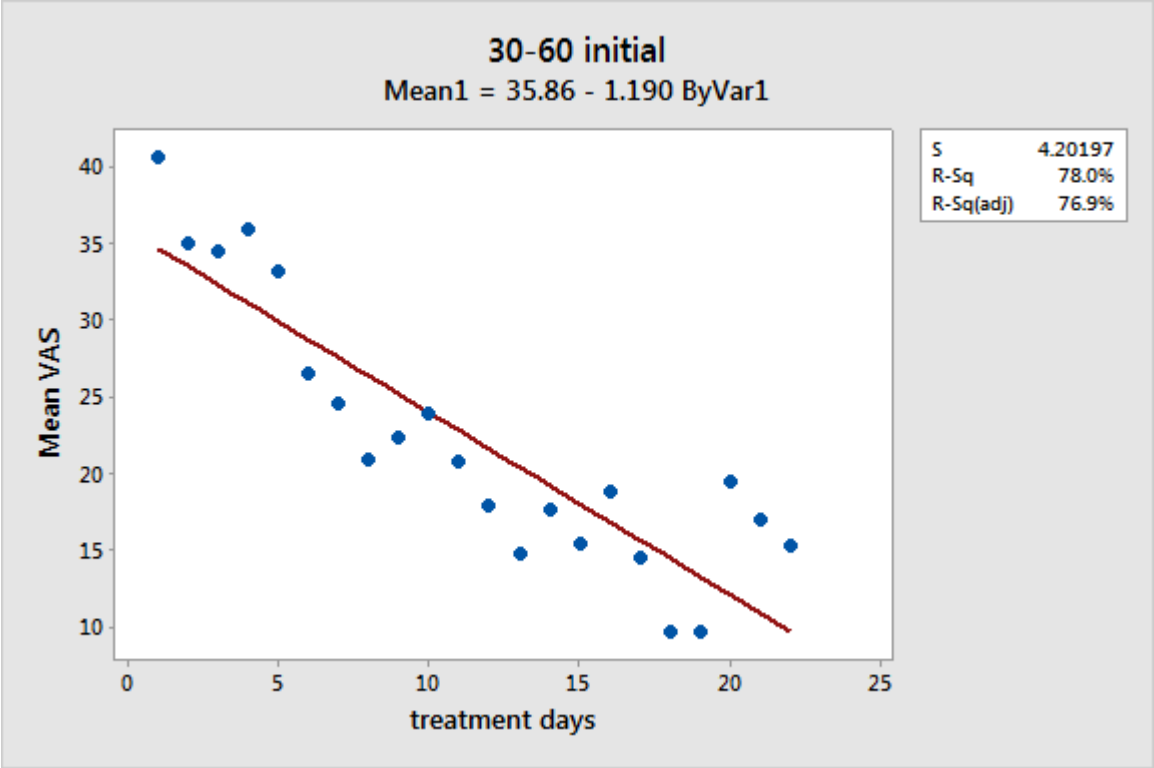


Figure 4. Trajectory of pain relief in those with high initial pain levels

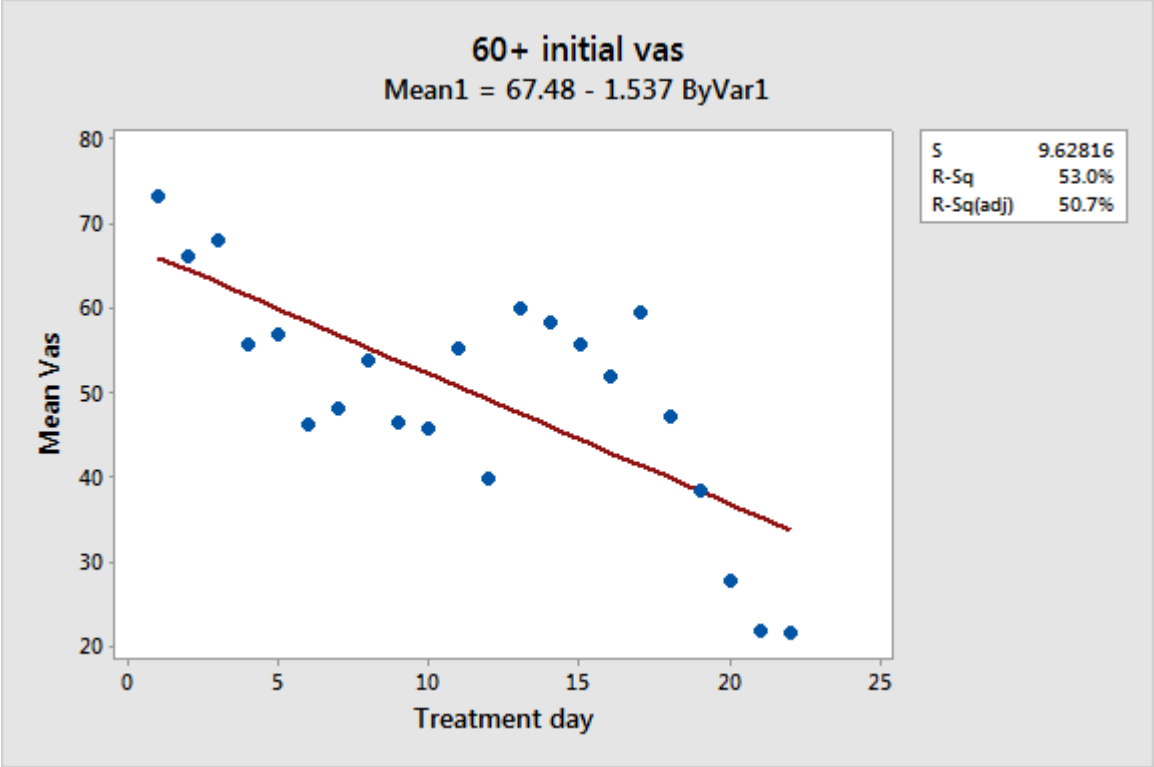


Figure 5. Dunnett comparison for low initial pain group.

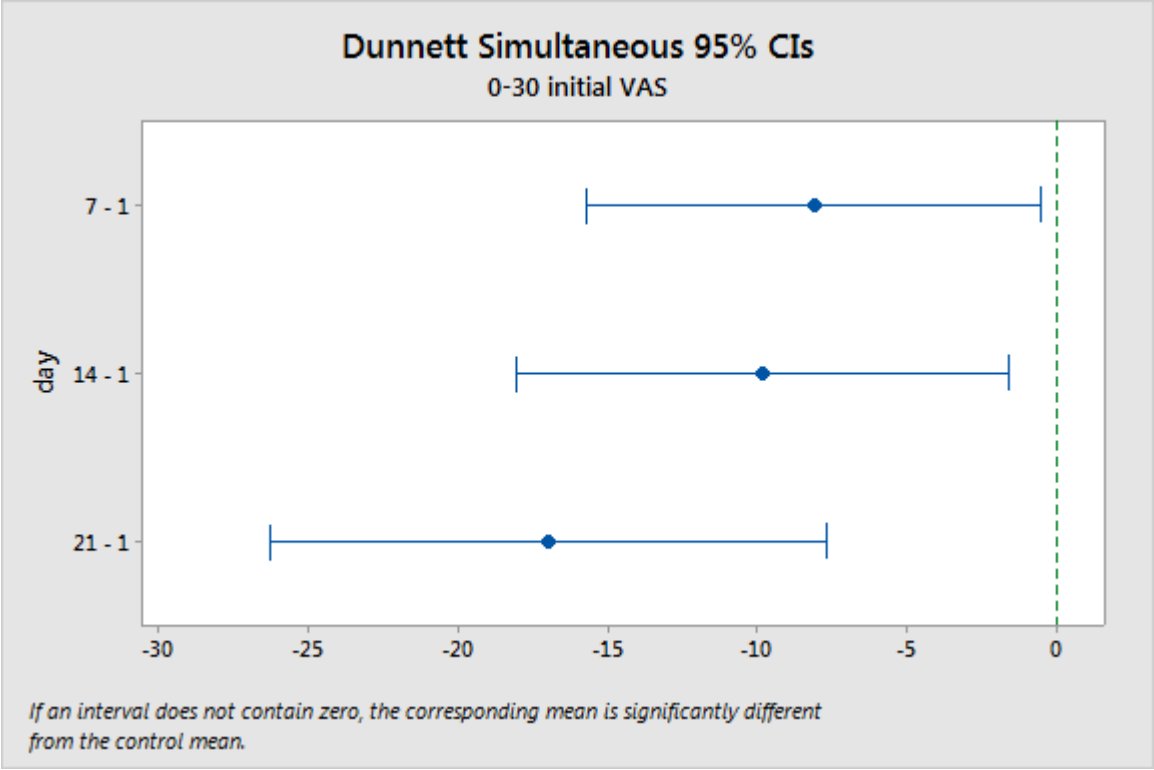


Figure 6. Dunnett comparison for medium initial pain group.

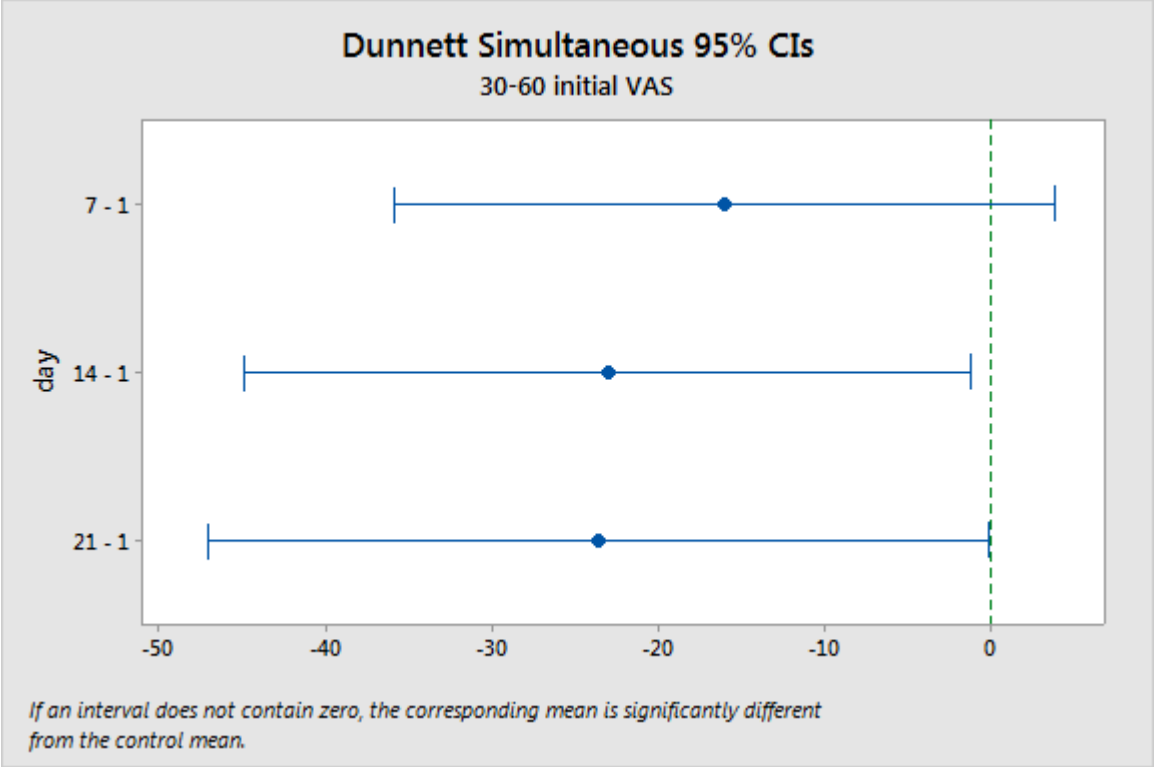
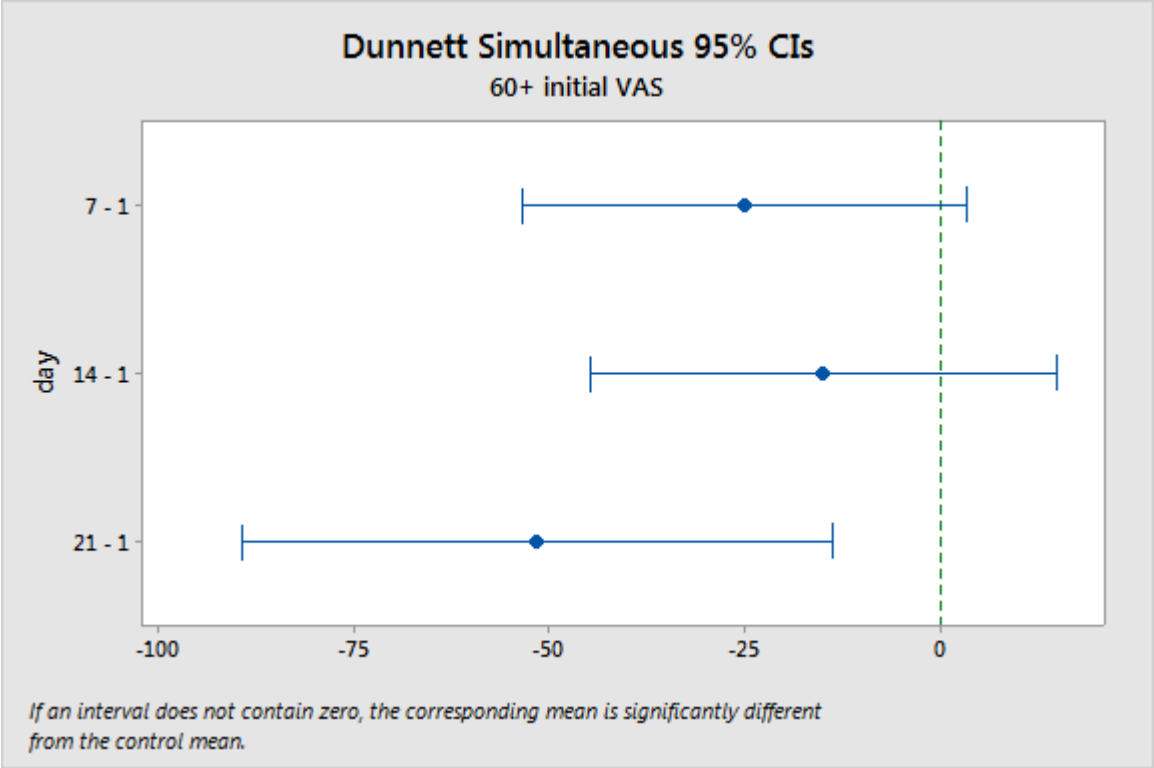


Figure 7. Dunnett comparison for high initial pain group.



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