

Acupuncture Improves Certain Aspects of Sleep in Hematopoietic Stem Cell Transplantation Patients: a Randomized Controlled Trial

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Research Article

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Abstract

Background

High-dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT) is associated with a high symptom burden including decrease in sleep quality. We conducted a randomized sham-controlled trial (#NCT01811862) to study the effect of acupuncture on sleep quality during HSCT.

Methods

Adult multiple myeloma patients undergoing inpatient and outpatient autologous HSCT were randomized to receive either true or sham acupuncture once daily for 5 days starting the day after chemotherapy. Sleep onset, total sleep time, sleep efficiency percentage, and sleep-onset latency time were assessed using an Actigraphy Sleep Monitor. A multi-variate regression analysis was conducted to compare the average area-under-the-curve of five acupuncture intervention days for each sleep outcome between groups, adjusted by baseline score and inpatient or outpatient chemotherapy stratum.

Results

Over 32 months, 63 patients were enrolled. Participants undergoing true acupuncture experienced a significant improvement in sleep efficiency when compared to sham (-6.70, 95% CI -13.15, -0.25, p=0.042). Subgroup analysis showed that the improvement is more prominent in the inpatient setting (-9.62, 95% CI -18.76, -0.47, p=0.040). True acupuncture produced noticeable yet non-significant improvement in sleep-onset latency times. Between-group differences in other sleep related variables were not statistically significant.

Conclusion

Our data suggest that true acupuncture may improve certain aspects of sleep, including sleep efficiency and possibly sleep-onset latency, in multiple myeloma patients undergoing HSCT. By studying patient reported outcomes in future larger scale studies, acupuncture's role in improving sleep quality during HSCT treatment can be further elucidated.

Introduction

Autologous hematopoietic stem cell transplantation (HSCT) (Or AHSCT) refers to the transplantation of the patient's own multipotent hematopoietic stem cells to reconstitute the bone marrow. Transplantation usually occurs two days after being treated with high dose chemotherapy and/or radiation therapy. This potentially curative treatment is used to treat hematologic and lymphoid malignancies[1]. Nearly two-thirds of the 30,000 autologous HSCT performed annually are used to treat multiple myeloma or non-Hodgkin's lymphoma [2, 3].

Despite the procedure's curative potential, high dose myeloablative conditioning chemotherapy is associated with numerous side effects including nausea, vomiting, fatigue, and disturbed sleep [1–8]. In specific, it is well documented that multiple myeloma patients undergoing HSCT frequently experience sleep disturbances, significantly hindering patients' quality of life. In fact, sleep quality is typically worse during inpatient treatment, and for nearly half of patients, sleep disturbances persist up to 6 to 12 months post-transplant [9–11]. Currently, symptom management during HSCT is mainly through pharmacologic treatment with hypnotic drugs. However, pharmacologic medications may have detrimental side effects such as over-sedation, memory decline, dependence, and withdrawal symptoms[12, 13]. Therefore, investigation of other potential treatment options is needed.

Acupuncture is an integrative medical modality involving the insertion of filiform needles into certain points on the body, accompanied with manual manipulation, electric impulse, or heat to stimulate therapeutic effects[14, 15]. Although the precise pathophysiology of acupuncture's therapeutic effect is still unclear, research suggests that the effects are mediated via modulation of the nervous system [16–19].

Some earlier studies have attempted to study the effect of acupuncture on insomnia. In a systematic review investigating the effect of acupuncture on sleep quality in 30 studies, pharmacotherapy control was used in 27 studies while sham/placebo was used in only three. It was suggested that acupuncture was superior to each of sham/placebo and pharmacotherapy in patients clinically diagnosed with

insomnia with no co-morbidities. However, further investigation was suggested since most studies were at high risk of bias and lacked blinding [20]. Similarly, in a study conducted by Frisk et al., it was found that 12 weeks of electroacupuncture (EA) resulted in an improvement (comparable to hormonal therapy) in several parameters of sleep quality in breast cancer patients with hot flashes. Nevertheless, it was unclear whether EA had a direct effect on sleep or indirectly by decreasing hot flashes[21]. Cognitive Behavioral Therapy for Insomnia (CBT-I) has also been shown to improve chronic insomnia. A recent study comparing CBT-I and acupuncture for insomnia in cancer survivors concluded that both CBT-I and acupuncture resulted in meaningful reductions in the severity of insomnia [22].

Those studies imply that acupuncture may have the potential to improve sleep quality, both broadly and in breast cancer patients; however, larger scale and less biased studies are still needed to better understand acupuncture's effect on insomnia. In addition, those studies were conducted in the setting of chronic insomnia, not insomnia associated with treatment of an acute illness, such as HSCT. We postulate that HSCT patient setting can influence the effect of acupuncture on sleep quality, because the patients are more ill and in the inpatient setting, patients are exposed to many sleep disrupting factors such as noise from other patients' rooms or staff conversations, increased light exposure, unfamiliar bed and environment, and night-time nursing schedule (checking vital signs, drawing blood, etc.) [23, 24]. We conducted a randomized sham-controlled trial with the primary objective of generating preliminary data regarding the effect of acupuncture on symptom burdens in this population. We also evaluated the effect of acupuncture on sleep quality.

Methods

Study Design

We conducted a prospective, parallel randomized, sham-controlled, blinded trial over 32 months[14]. Sham acupuncture was used as the control to account for effect from attention and interaction with the therapist. The research protocol was approved by the Institutional Review Board at MSKCC and registered at clinicaltrials.gov before subject enrollment. The trial was registered at www.clinicaltrials.gov as #NCT01811862.

Study Subjects

Eligible Multiple Myeloma patients undergoing inpatient and outpatient high dose melphalan chemotherapy followed by HSCT at MSK were screened and approached for written informed consent. Patients were enrolled if they met the following criteria: aged above 21 years old, diagnosed with multiple myeloma, and scheduled to receive high dose myeloablative conditioning chemotherapy followed by upfront or salvage autologous peripheral blood hematopoietic stem cell transplant. Exclusion criteria included any acupuncture treatment in the preceding 4 weeks prior to Day 1, an absolute neutrophil count (ANC) less than 200/ μ l due to higher risk of infection, and a platelet count less than 20,000/ μ l due higher to risk of bleeding.

As an exploratory study to generate preliminary data for future randomized controlled trial, we defined the sample size as 60 in consideration of 5% of the participants who may drop off and loss of follow-up.

Randomization

Randomization was done using the MSKCC's Clinical Research Database (CRDB), an institution-wide computer program used to achieve allocation concealment in all randomized trials at MSKCC. Patients were randomized to true or sham acupuncture using blocks of randomly permuted length, stratified by whether the HSCT was done in an inpatient or outpatient setting. Patients and clinical evaluators were blinded to group assignment. Only the treating acupuncturist was informed of treatment allocation.

Intervention

All study participants received the same standard pre and post transplantation care as other Multiple Myeloma patients undergoing conditioning chemotherapy in preparation for autologous HSCT at MSK. All participants received conditioning chemotherapy on day - 2 and stem cell infusion on day 0. Participants received either true or sham acupuncture from day -1 to day 3, marking 5 days in total. Observation took place on days 4 and 5. The 5-day intervention continued sequentially until any of the following occurred: patients became neutropenic, ANC dropped below 200/ μ l or platelet count dropped below 20,000/ μ l.

Licensed acupuncturists provided 20-minute acupuncture treatment session once daily either in the patient's hospital room for in-patients or at the clinic for out-patients. Through literature review of previous studies and by consensus among the acupuncturists, the following acupuncture points were selected: GV20 (Bai Hui), Ex-HN3 (Yin Tang), HT7 (Shen Men), PC6 (Nei Guan), ST36 (Zu Sanli), SP6 (San Yin

Jiao), KI3 (Tai Xi), LR3 (Tai Chong), and Ear Shen Men. The acupuncture needles used were manufactured by Seirin Corporation (Shizuoka, Japan) with the following dimensions: 36 gauge × 40 mm length and 40 gauge × 30 mm length. Neither electric stimulation nor heat was applied to the needles.

Sham acupuncture was performed using a previously validated method at a bony area next to each acupoint, with a frequency and duration identical to true acupuncture, except the actual insertion of the needles into the skin[25, 26]. Each acupuncturist would tap an empty plastic acupuncture needle guide tube on the bony area next to each acupuncture point to produce some discernible sensation. Then, a needle was tapped with a piece of adhesive tape to the dermal surface for approximately 20 minutes. The patients' eyes were covered with patches in both groups to ensure proper participant blinding.

Evaluation

Objective measurement of sleep quality was recorded using a validated wristband actigraph-based sleep monitor (Actiwatch by Philips) starting at noon and ending 24 hours later[27–29]. Baseline assessments were obtained within the 1-2 weeks before chemotherapy and hematopoietic stem cell transplantation. The device samples a wearer's movement at 32Hz using an accelerometer and uses proprietary software to calculate the following values for the five aspects of sleep: number of awakenings, wake time after sleep onset (in minutes), total sleep time (in minutes), sleep efficiency percentage (%) and sleep-onset latency time (in minutes) from Day -2 to 5[28].

Masking

Participants were blinded to treatment allocation. Research assistants, laboratory personnel, and statisticians were blinded to group assignments, collected study outcomes, and analysis. Only acupuncturists were aware of a patient's group assignment. At the end of the study, effectiveness of blinding was assessed by asking patients to guess to which group they were assigned to.

Data Analysis

If a participant provided both baseline and Day 5 assessments, she or he was deemed evaluable for study outcomes. Patients' data was analyzed according to intention to treat, irrespective to how many treatments they received. We used Stata 12 (StataCorp, College Station, TX) to perform all data analyses.

When the actigraph-based sleep monitor was validated against polysomnography (PSG – considered the gold standard in sleep evaluation), the Pearson r values for actigraphy and PSG revealed moderate to strong correlations on all measured sleep values except sleep-onset latency time : number of awakenings ($r=0.49$), wake time after sleep onset ($r=0.48$), total sleep time (0.70) sleep efficiency percentage (0.43) and sleep-onset latency time (0.30)[27].

For statistical analyses, we calculated the average area under the curve of five acupuncture intervention days for each sleep outcome. Data was evaluated by repeated measures ANOVA. A multi-variate regression analysis was conducted using Stata 12.0 to compare outcomes between the sham and acupuncture group, adjusted by baseline score and inpatient or outpatient chemotherapy stratum. When analyzing the interaction of the acupuncture group and inpatient or outpatient group in the model, if the interaction was significant, a subgroup analysis was performed.

Confidentiality

All gathered information was stored in a secure location in facilities of the Integrative Medicine Service. The data collected for this study was entered into a secure clinical research database (CRDB). Source documentation is available to support the computerized patient data. The confidentiality of patient information was carefully protected.

Results

The flow of study participants throughout the trial is illustrated in the CONSORT diagram (Fig. 1). Among the 63 randomized participants, 2 withdrew consent before receiving the true acupuncture intervention and 1 withdrew after receiving the sham acupuncture intervention without providing the primary endpoint. Among the 60 evaluable patients, data from 29 participants in the true acupuncture group and 31 from the sham acupuncture group were analyzed. Patient characteristic by treatment arm is shown in Table 1.

Sleep changes during HSCT between sham and acupuncture groups (Pooled analysis: outpatients and inpatients non-segregated)

Figure 2 illustrates two-way line charts comparing acupuncture vs sham in each of the five measured parameters of sleep: total sleep time, sleep-onset latency time, awakening times, wake time after sleep onset, and sleep efficacy. Statistical analysis was completed by measuring the area under the curve. Outcomes were compared between sham and acupuncture group, adjusted by baseline score and inpatient or outpatient chemotherapy stratum using a regression model.

As shown in figure 2, overall, our results indicate that acupuncture has the potential to improve each of the sleep parameters except for awakening times. Concerning awakening times, almost no difference was found among the two groups (Fig. 2A). As for sleep-onset latency time, the acupuncture group had a shorter latency time than sham acupuncture, but not statistically significant (-20.92, p=0.4) (Fig. 2B). Similarly, it was observed that the acupuncture group had a better total sleep time when compared to sham (11.72, p=0.13) (Fig. 2C) and a noticeably higher WASO (-10.95, p=0.055) (Fig. 2D). However, in both parameters, the mean differences did not achieve statistical significance. In contrast to the previously mentioned parameters, the acupuncture group had a statistically significant higher sleep efficiency than the sham group (-6.70, p=0.042) (Fig. 2E).

Sleep changes during HSCT between groups in outpatient vs. inpatient setting

Sleep efficiency was significantly better in the acupuncture group when compared to sham. To investigate further whether this difference persists when considering patient setting, a subgroup analysis was performed as shown in Table 2. We found that sleep efficiency score improved significantly in the acupuncture group in inpatient subgroup (-9.62, p=0.040) but not in outpatients (-0.95, p=0.8). The difference in the inpatient subgroup was higher than the pooled difference mentioned earlier (-6.7, p=0.042). As for sleep-onset latency time, the difference between acupuncture and sham groups nearly doubled in the inpatient subgroup (21.84 in inpatients vs. 11.72 in pooled analysis), approaching but not reaching statistical significance (p=0.054). Concerning WASO, no improvement was seen in the inpatient subgroup. There was a non-significant difference in the outpatient subgroup (difference in outpatient= -6.28 vs -10.95 in pooled analysis). As for awakening times, like the pooled analysis, no difference was detected in the inpatient subgroup between sham and acupuncture, but in outpatients, a small improvement was detected (difference sham-acupuncture= -6.28, p=0.2). Concerning sleep time, acupuncture still showed a noticeable improvement when compared to sham and this difference although non-significant, remained similar when pooled or stratified to inpatient and outpatient subgroups. Within outpatients, there were no significant changes between the two arms. Between-group differences in other sleep related variables were not statistically significant.

Safety of Acupuncture

Patients were monitored daily for side effects by the inpatient team. Acupuncture was shown to be well tolerated, with no significant differences in incidence of adverse events related to acupuncture between the two groups. There were 2 patients in the sham acupuncture group admitted to the intensive care unit (ICU) for events deemed unrelated to the sham acupuncture procedure. None of the patients in the true acupuncture group were admitted to the ICU.

Discussion

In this randomized control trial, we examined the role of acupuncture as an integrative treatment to help manage sleep disturbances in multiple myeloma patients undergoing HSCT. Our data suggest that true acupuncture may significantly improve sleep efficiency in this population, especially in the inpatient setting. Our results also showed a trend that acupuncture can noticeably improve sleep-onset latency time in this population despite not achieving statistical significance.

One of the strengths of our study is that our study was in a population of cancer patients known for their high symptom burden. Most of the previous studies of acupuncture on insomnia were conducted on non-cancer patients [30]. Only a few studies included insomnia patients with comorbidities such as stroke, end-stage renal disease, perimenopause, pregnancy, and psychiatric diseases [30]. A few studies investigated the effect of acupuncture on sleep quality in cancer patients. In a systematic review conducted by Choi et al in 2017, 6 studies investigated the effect of acupuncture on insomnia in cancer patients[30]. It was not clear whether acupuncture has a similar effect in an acutely ill population who experience complex symptom clusters. HSCT preceded by high dose chemotherapy causes significant acute side effects, including pain from mucositis, poor appetite, fatigue, disturbed sleep, nausea, vomiting, and diarrhea[4, 31], which contribute or exacerbate insomnia. Our study suggests acupuncture can have an effect in this clinical setting.

Because acupuncture can reduce some the symptoms, such as pain, nausea, and vomiting [14, 32], we are not sure if acupuncture improves sleep quality directly or indirectly by reducing contributing symptoms, as our previous manuscript showed that acupuncture can reduce these symptoms. This can be something interesting to investigate in future studies.

Subgroup analysis showed that the significant improvement in sleep efficiency persisted in inpatients only. Within outpatients, there were no significant changes between the two arms. The decision to treat a patient in the inpatient setting was provider and patient dependent. Usually, choosing a patient setting is made due to lack of a caregiver for outpatient transplantation or the presence of an existing comorbidity that requires close monitoring (i.e. renal dysfunction). It is well known that inpatients are more likely to experience sleep disrupting factors during their hospital stay, which include noise from visitors and medical staff nearby, excessive light exposure, unfamiliar surroundings, night vital sign checking, and blood drawing [23, 24]. These factors commonly disrupt normal circadian rhythm leading to a decrease in sleep quality [33, 34]. Studies suggest that even if the total number of sleep hours in a day can approach normal at the hospital, half of sleep occurs during daytime and in interrupted short intervals[33, 34]. Patients in the inpatient setting might have received more medications that could influence sleep such as antiemetics or sleep aids. Our results show that acupuncture may have a stronger effect in the inpatient setting.

Another strength of our study is that we used sham acupuncture, instead of usual care, as control In the systematic review conducted by Cheuk et al., among 15 studies with needle acupuncture as an intervention, only 3 of those studies included sham as a control [35]. However, none of these studies had proper blinding or allocation concealment. Two out of the three studies had a moderate to high attrition bias. In contrast, our study was properly blinded. At the end of our study, effectiveness of blinding was assessed by asking patients to guess their allocation. Patients had a 50% chance of getting the right answer. Our loss to follow up rate was low (4.8%). Therefore, our data adds to the existing limited evidence by providing data collected from a well blinded and low attrition study.

Acupuncture was safe with minimal attributable adverse events. These findings may suggest that acupuncture has the potential to help manage sleep disturbances in patients undergoing HSCT without adding more burden or serious adverse effects during the procedure.

A few limitations were present in our study. First, our study had a small sample size. This study was powered to estimate the effect size of acupuncture on symptom burdens, not to definitively prove the efficacy of acupuncture by rejecting a null hypothesis. The second limitation is that sleep quality was a secondary outcome. Secondary outcomes or confounding variables could have led to a false discovery. Secondary findings need to be interpreted and require further verification. To verify these findings, a larger trial should be conducted. Another limitation is that a usual-care control group was not included. Usual care control would give us info on real world effect size as in clinical practice. Our study's generalizability is also limited. We did not include allogeneic HSCT patients because their course is too heterogeneous for a study of a small sample size.

Despite the limitations, to our knowledge this is the first randomized controlled trial examining acupuncture as an integrative approach for improving certain aspects of sleep in the HSCT setting. Future studies will shed more light on the effect of acupuncture on sleep quality in patients who are acutely ill, especially those admitted to a hospital.

Conclusion

In conclusion, we found that true acupuncture may improve certain aspects of sleep quality in multiple myeloma patients receiving autologous HSCT. Specifically, acupuncture was found to improve sleep efficiency significantly when compared to sham acupuncture in our study, particularly in the inpatient setting. There was also a trend of reduced sleep-onset latency time. Future research with an adequate sample size targeting specific aspects of sleep quality and patient report outcomes, may help elucidate acupuncture's role in improving sleep quality during HSCT treatment, possibly expanding treatment options available to patients during the difficult time of transplant.

Declarations

Funding

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Conflict of Interest/Competing Interests

Dr. Giralt has received research funding from Amgen, Janssen, Celgene, Quintiles, Pfizer, CSL Behring, Sanofi, Adienne, Kite, JAZZ, and Actinium. The remaining authors declare no competing financial interests.

Availability of data and material:

Data not publicly available. Limited access to data due to expiration of study protocol.

Code availability

Not Applicable

Author's contribution statement

All authors whose names appear on the manuscript have made substantial contributions to the design of the work, analysis and interpretation of data, drafting the manuscript, and revision for important intellectual content. All authors approve the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical approval

This study was reviewed and approved by the Institutional Review Board (IRB) at Memorial Sloan Kettering Cancer Center. All procedures performed in the trial were in accordance with the ethical standards of the IRB committee and the 1964 Helsinki declaration or comparable ethical standards.

Consent to participate

Informed consent was obtained from all participants included in the study.

Consent for publication

Not Applicable

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Tables

Table 1
Patient Characteristics (age gender, patient setting) by treatment (n=60)

	Acupuncture (n = 29)	Sham acupuncture (n = 31)
Age, y	59 (54, 66)	58 (55, 64)
Male	10 (34%)	12 (39%)
Inpatient chemotherapy	16 (55%)	18 (58%)

Table 2
Subgroup analysis of sleep quality scores in inpatients vs. outpatient

	Inpatient						Outpatient				
	Sham	Acupuncture	Inpatient Difference	95% C.I.	P value	Sham	Acupuncture	Outpatient Difference	95% C.I.	P value	
Sleep Efficiency	66.65 (16.27)	69.00 (22.59)	-9.62	-18.76, -0.47	0.040	61.30 (29.73)	54.50 (38.26)	-0.95	-9.73, 7.84	0.8	
Sleep-onset latency time	41.88 (38.06)	20.24 (13.62)	21.84	-0.37, 44.05	0.054	33.48 (35.73)	23.48 (20.94)	-5.32	-22.53, 11.89	0.5	
WASO	28.39 (9.68)	26.89 (11.90)	-0.04	-6.61, 6.54	1	26.94 (14.43)	25.18 (21.35)	-6.28	-16.84, 4.28	0.2	
Awakening Times	28.39 (9.68)	26.89 (11.90)	-0.04	-6.61, 6.54	1	26.94 (14.43)	25.18 (21.35)	-6.28	-16.84, 4.28	0.2	
Total Sleep Times (min.)	371.11 (102.02)	352.50 (132.65)	-17.35	-80.01, 45.31	0.6	320.26 (160.32)	300.26 (214.91)	-23.99	-100.82, 52.83	0.5	

*Adjusted by baseline, interaction between acupuncture group and inpatient/outpatient stratify was not significant for all outcomes

Figures

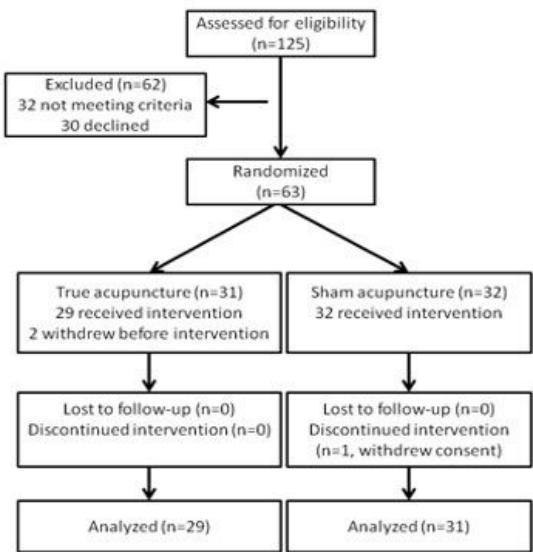
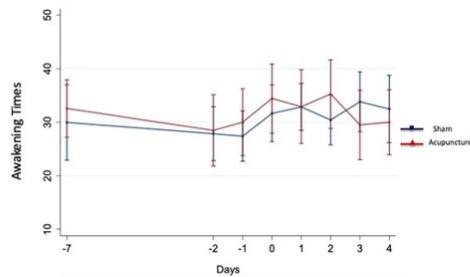
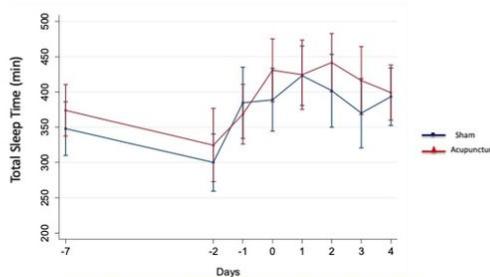


Figure 1

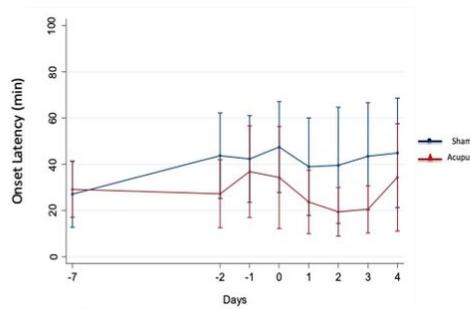
CONSORT diagram of study design and enrollment



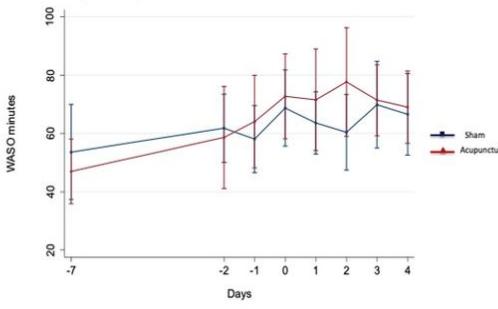
A Difference: -1.95, 95% CI -7.38, 3.49, p=0.5



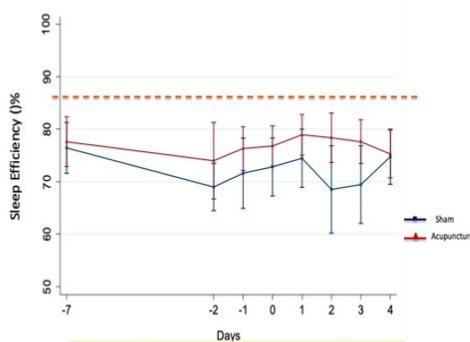
B Difference: -20.92, 95% CI -66.28, 24.44, p=0.4



C Difference: 11.72, 95% CI -3.64, 27.07, p=0.13



D Difference: -10.95, 95%CI -22.16, 0.27, p=0.055



E Difference -6.70, 95% CI -13.15, -0.25, p=0.042

Figure 2

Two-way line charts comparing acupuncture vs sham in each parameter of sleep measured: A: Awakening Time, B: Total Sleep Time, C: Sleep Onset Latency Time, D: WASO (Wake Time After Sleep Onset), E: Sleep Efficacy. *Below each graph is the difference in means between groups*