CLINICAL ACUPUNCTURE TRIAL ON INSOMNIA PATIENTS---A TAIWAN EXPERIENCE

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Objective: The aims of this study were to examine whether acupuncture is better than/same as Stilnox (Generic name-Zolpidem) and whether combination of acupuncture with Stilnox is better than/same as acupuncture alone or Stinox alone. **Methods**: A randomized controlled trial was conducted from August 2007 to May 2008 in Zhong-Xing Branch , Taipei City Hospital, Taiwan. The participants were randomly assigned into one of the three groups for a 4-week intervention and a 4-week follow-up after treatments. Treatment of the participants was given on a weekly basis. Group A took Stilnox 5mg/day at bedtime. Group B took Stilnox 5mg/day at bedtime and received acupuncture 3 times a week. Group C took no medication but received acupuncture 3 times a week. The effectiveness of treatments of the three groups was all evaluated weekly by the Pittsburgh sleep quality index (PSQI). **Results:** A total of 48 participants were initially enrolled. Among them, 28 withdrew during the study. The remaining 20 participants, including 2 of Group A, 10 of Group B and 8 of Group C, completed the entire treatment course and were evaluated. The result showed that the PSQI value decreased significantly ($p < 0.05$) compared with baseline after 3-week intervention and 4-week intervention in both Group B ($n = 10$) and Group C ($n = 8$). The effects of treatments were still maintained at the 4-week follow-up after treatments. There was no significant difference($p = 0.73$) in terms of effectiveness of treatment between Group B and Group C. **Conclusions**: The effectiveness of acupuncture alone or in combination with Stilnox remains uncertain, because of the small sample size and high drop-out rate, especially in the medication-only group. The initial data may reveal potential beneficial effects of acupuncture in treating insomnia.

Key words: insomnia, acupuncture, pittsburgh sleep quality index (PSQI)
Trial registration: current Controlled Trials ISRCTN07857866
Abbreviations: GV=Governor Vessel; GB=Gallbladder Meridian; PC=Pericardium Meridian; LI=Large Intestine Meridian; ST=Stomach Meridian; SP=Spleen Meridian; LR=Liver Meridian; GI=Gastrointestinal

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Introduction

Insomnia is a subjective complaint of poor sleep, which may produce impairment in daytime function or mood. This definition encompasses complaints of insufficient sleep, difficulty in initiating or maintaining sleep, interrupted sleep, poor quality or non-restorative sleep or sleep that occurs at the wrong point in the day-night cycle[1].

Since there is no established definition of "normal" sleep, estimated prevalence of insomnia may vary widely. Different population-based studies estimate that 10% to 40% of American adults have intermittent insomnia; and 10% to 15% have long-term sleep difficulties[2]. The prevalence rate of insomnia in Taiwan reaches 15%[3]. Although insomnia is highly prevalent, sleep disturbance often go unrecognized and untreated, quite possibly because providing effective treatment is a continuing challenge for healthcare providers[4].

Given the multi-factorial nature of insomnia, treatment approaches are numerous. Underlying medical or psychiatric conditions should be treated in the first place. However, it is not always possible to eliminate or alleviate the primary disease process. In such situations, the treatment approach is to focus on intervention that will positively promote sleep. Many pharmacological treatments are available for treating insomnia. However, pharmacological treatments have not been conclusively shown to be effective and adverse effects are not uncommon[5, 6]. Owing to the pitfalls of the usual pharmacological and psychological approaches to treatment of insomnia, alternative therapies such as acupuncture have been increasingly used by patients.

Acupuncture is one of the major modalities of treatment in Traditional Chinese Medicine. It involves complex theories of regulation of Yin and Yang forces, Qi, blood and body fluids. According to Traditional Chinese Medicine, an imbalance in the Yin and Yang forces of the body, or an excess or a deficiency of Qi, blood or body fluids, are the main causes of pain or diseases. Acupuncture treats illness by re-establishing the balance between the Yin and Yang forces and restoring normal Qi, blood and body fluids through stimulation of different meridian points that govern different parts of the body and their interaction[7].

Being a relatively simple, inexpensive and safe treatment, acupuncture is widely used as an alternative treatment approach to various neurological disorders[8]. There are anecdotal reports suggesting that acupuncture may improve sleep and relieve insomnia. However, it remains uncertain whether the existing evidence is scientifically rigorous enough for acupuncture to be recommended for routine use in patients with insomnia. Well-designed clinical trials are needed to further investigate the efficacy and safety of acupuncture for the treatment of insomnia[9].

The aims of this study were to examine whether acupuncture is better than/same as Stilnox (Generic name-Zolpidem) and whether combination of acupuncture with Stilnox is better than/same as acupuncture alone or Stilnox alone. Hence, we conducted this randomized controlled study under conditions similar to routine treatment.

Methods

Adult sleep-disorder participants of chronic insomnia were recruited from August 2007 to May 2008 in Taipei City Hospital, Taiwan. Recruitment

efforts were targeted at communities located in Taipei city. Announcements about this study, approved by the Taipei City Hospital Institutional Review Board, were placed on bulletin boards of Taipei City Hospital and district health centers in Taipei. The inclusion criteria of this study were: (1) adult poor sleepers (aged above 20 years), who have frequent sleep quality disturbance for more than three nights and that lasts for more than one month , and (2) those who have not taken any sleep medications associated with psychiatric disorders within 30 days. On the other hand, those who feared having needles inserted into their bodies, were pregnant, or had central nervous system diseases such as seizure disorder, cerebrovascular disease, dementia and any other conditions deemed unsuitable for trial as evaluated by the physician in charge, were excluded in this study.

Interested individuals could directly contact the research assistant, who explained the purpose and details of participation in the study. After filling in the informed consent, baseline data and PSQI questionnaires[10], participants were enrolled and listed by time sequence. According to the list sequence, the research assistant gave each participant a number by 1 2 3, 1 2 3,…serial order. Number 1 was assigned to Group A, number 2 Group B, number 3 Group C, for a 4-week intervention and a 4-week follow-up after treatments.

Treatment of the participants was delivered and evaluated on a weekly basis. The participants of the medication therapy group (Group A) took Stilnox (Generic name-Zolpidem) 5mg/day at bedtime prescribed by a psychiatric doctor weekly. The participants of the combined medication and acupuncture therapy group (Group B) took Stilnox 5mg/day at bedtime and received acupuncture 3 times a week. The participants of the acupuncture therapy group (Group C) received acupuncture 3 times a week performed by a Traditional Chinese Medicine doctor.

The acupuncture points included Baihui (GV 20), Sishencong (Extra 6), Fengchi (GB 20), Neiguan (PC 6), Hegu (LI 4), Zusanli (ST 36), Sanyinjiao (SP 6), and Taichong (LR3). During the acupuncture session, needles were inserted in the above points bilaterally. The needles used were 40 mm long and 0.30 mm in diameter. After the needles were inserted into the acupuncture points and the patients had sensation, they were retained in the points for 30 minutes.

The effectiveness of treatments of the three groups was all evaluated weekly by the PSQI[10]. PSQI is a self-rated questionnaire, which assesses sleep quality and disturbance during the past month. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. In this study, we used the PSQI for both the initial assessment and the on-going weekly comparative measurements to examine the effectiveness of different treatments for insomnia. We also recorded in each session all adverse side effects reported by the participants.

In this study, we used SPSS 11.0 and SAS 9.1 version of statistical analysis software for pair t test of PSQI scores and the mixed model for repeated measurements. Pair t test was employed to compare the PSQI scores between data of different treatment intervals and baseline data within each group. The mixed model was utilized to examine the difference

in decreased PSQI value related to the effectiveness of treatment between groups.

Results

Reasons of withdrawal

Although many people complain of frequent sleep quality disturbance, 33 of 99 poor sleepers recruited refused to participate in the Randomized Clinical Trial (RCT) and another 18 poor sleepers who hadn't met the inclusion criteria were excluded. A total of 48 participants were initially enrolled and randomly assigned into three groups in the study. Among them, 28 withdrew during the study: 10 participants (2 in Group A, 3 in Group B, 5 in Group C) could not receive treatment arranged on schedule because of work or business travels; 9 participants (7 in Group A, 2 in Group B) withdrew because they were concerned about the potential side effect of hypnotics and refused to take medicine every day after their sleeping quality was improved; 4 participants (in Group A) withdrew as advised by the psychiatrist because of the adverse effect of medication; 3 participants (in Group C) withdrew because they took hypnotics during the study; and 2 participants (1 in Group A , 1 in Group B) withdrew because they were not satisfied with the therapeutic outcome. The remaining 20 participants, including 2 of Group A, 10 of Group B and 8 of Group C, completed the entire treatment course and were evaluated. Figure 1 is the flowchart trial profile that summarizes the study process.

Demographic characteristics of participants

A total of 48 participants (26 female and 22 male) were initially enrolled. The demographic profile was seen as in Table 1. Among them, 20 (11 female and 9 male) completed the study. In Group A, the mean age of participants was 53 years and the mean insomnia duration was 43 months (range 14-72 months). In Group B, the mean age of participants was 56 years (31-71 years) and the mean insomnia duration was 110 months (range 7-360 months). In Group C, the mean age of participants was 53 years (42-82 years) and the mean insomnia duration was 98 months (range 19-240 months).Those participants all hadn't taken any medications within 2 months when recruited and hadn't had any underlying medical conditions causing insomnia, e.g., chronic diseases, chronic pain, etc. The demographic characteristic of participants who completed the study was seen as in Table 2.

Outcome measurements

There were only 2 participants remaining in Group A. So the data from Group A is essentially useless and further analyses would be confined to Groups B and C. In Table 3, the pretest-posttest PSQI value of participants in Group B and Group C at different treatment intervals showed that the PSQI value decreased significantly ($p < 0.05$) compared with baseline after 3-week and 4-week intervention in both Groups B and C. Because the participants all complied with the protocol and hadn't received any forms of treatment during the 4 week period from the end of intervention to final evaluation 4 weeks after completion of study treatment. In Table 4, the decrease in PSQI value between groups B and C examined by the mixed model showed that the effects of treatment were still maintained in both Group B and C at 4-week follow-up after completion of

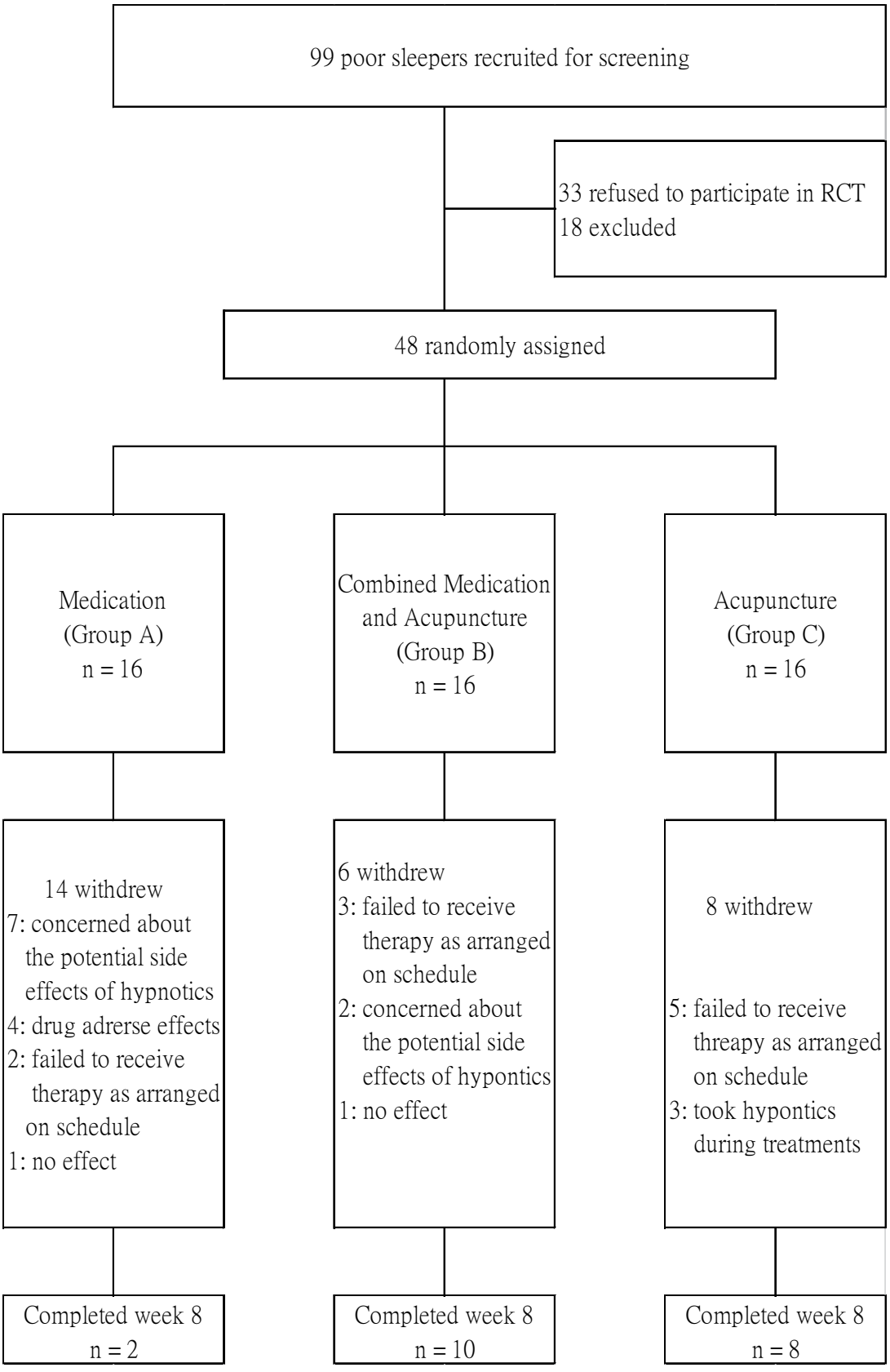

Fig. 1. Trail profile and design.

Table 1. Demographic characteristics of participants enrolled

Variable	Total (N=48)	Group A (N=16)	Group B (N=16)	Group C (N=16)	P-value
Gender (%)					0.37
Female	54	50	44	69	
Male	46	50	56	31	
Age Mean (SD)	54(11)	55(12)	52(13)	56(12)	0.75
Have job (%)	45	44	56	37	0.66
Insomnia duration (month) Mean (SD)	98(76)	78(52)	110(97)	98(78)	0.71
Life habits					
Smoke (yes, %)	35	38	44	25	0.50
Drink (yes, %)	42	44	50	31	0.74
Tea (yes, %)	46	44	56	38	0.83
Coffee (yes, %)	38	38	44	31	0.72
Exercise (yes, %)	75	69	81	75	0.78
Nap (yes, %)	42	44	38	44	1.00
Methods ever used (%)					
Acupuncture	31	38	25	31	0.83
Exercise	38	31	44	38	0.91
Drug	67	69	56	75	0.89
Relax training	17	13	13	25	0.79
Pretest PSQI Mean (SD)	13.18(1..48)	12.34(1.31)	13.92(1.23)	13.48(2.21)	0.33

A: Medication B: Medication combined with Acupuncture C: Acupuncture

treatment. There was no significant difference (p＝0.73) in terms of effectiveness of treatment between Group B and Group C. In addition, 8 participants (5 in Group B and 3 in Group C) had ever expressed having better quality of sleep in the night after receiving acupuncture during treatment session.

Adverse effects

After taking Stilnox at bedtime, seven of the 32 participants experienced adverse effects: 4 in Group A developed severe headache and withdrew from the study as advised by the psychiatrist, 1 in Group A experienced fatigue the following morning, 1 in Group B felt dizzy, and 1 in Group B had epigastric discomfort. Most of the adverse effects were noted in the first week after medication treatment. On the other hand, 2 of the 32 participants developed ecchymosis on acupuncture points LI4 (in Group B) and PC6 (in Group C) during treatment session. No other adverse effects in association with the acupuncture treatment were noted.

Discussion

Insomnia is a common sleep disorder with devastating socioeconomic consequences. Most of the patients are treated with medications. In order to avoid the possible interfering effects of hypnotics,

Table 2. Demographic characteristic of participants who completed the study

Variable	Total (N = 20)	Group A (N = 2)	Group B (N = 10)	Group C (N = 8)
Gender (%)				
Female	55	50	40	75
Male	45	50	60	25
Age Mean (SD)	57(14)	53(0)	56(15)	60(14)
With job (%)	40	50	50	25
Insomnia duration (month)Mean (SD)	98(100)	43(41)	110(112)	98(98)
Life habits				
Smoke (yes, %)	5	0	0	13
Drink (yes, %)	20	50	20	13
Tea (yes, %)	45	50	50	38
Coffee (yes, %)	30	0	45	25
Exercise (yes, %)	90	100	80	100
Nap (yes, %)	45	50	40	50
Methods ever used (%)				
Acupuncture	30	0	30	38
Exercise	70	50	70	75
Drug	70	0	80	75
Relax training	20	50	10	25
Pretest PSQI Mean (SD)	13.35(2.48)	11(1.41)	13.90(1.73)	13.25(3.24)

A: Medication B: Medication combined with Acupuncture C: Acupuncture

Table 3. The pretest-posttest PSQI value of participants in Group B and Group C at different treatment intervals

Variable	Treatment interval (week)	Pretest PSQI (A)	Posttest PSQI (B)	Difference (B-A)	SD	P value
Group B (n = 10)	0－1	13.90	12.10	-1.80	3.74	0.1619
	0－2	13.90	11.10	-2.80	3.36	0.0271
	0－3	13.90	9.00	-4.90	3.41	0.0014
	0－4	13.90	6.60	-7.30	5.23	0.0017
	0－8	13.90	5.80	-8.10	2.77	< .0001
Group C (n = 8)	0－1	13.25	11.13	-2.12	2.90	0.0769
	0－2	13.25	9.63	-3.62	4.72	0.0663
	0－3	13.25	10.63	-2.62	2.33	0.0152
	0－4	13.25	9.88	-3.37	3.74	0.0379
	0－8	13.25	11.13	-2.12	3.60	0.1392

Table 4. Decrease in PSQI value between Groups B and C examined by the mixed model

Variable	Estimate	SE	T	P value
Intercept	13.90	1.26	11.01	<.0001
Group C (ref.= Group B)	-0.65	1.89	-0.34	0.7332
week1 (ref.=week0)	-1.80	1.24	-1.45	0.1511
week2	-2.80	1.24	-2.25	0.0269
week3	-4.90	1.24	-3.95	0.0002
week4	-7.30	1.24	-5.88	<.0001
week8	-8.10	1.24	-6.52	<.0001
Group C after1-week intervention	-0.33	1.86	-0.17	0.8619
Group C after2-week intervention	-0.83	1.86	-0.44	0.659
Group C after3-week intervention	2.28	1.86	1.22	0.2255
Group C after4-week intervention	3.93	1.86	2.11	0.0382
Group C at 4-week follow-up	5.98	1.86	3.21	0.0019

Group B: Medication combined with Acupuncture Group C: Acupuncture

this randomized clinical study targeted the sleep-disturbed persons who had not taken any sleep medications associated with psychiatric disorders within 30 days. In Taipei, almost all residents are covered by the National Health Insurance. It is convenient and easy for people to receive acupuncture or medication treatments. Those two kinds of treatment approaches are too different to be compatible as control. Most people (33 of 99 poor sleepers in this study) did not like being treated randomly as "guinea pigs" and refused to participate in the Randomized Clinical Trial (RCT). Since most people in Taiwan have the experience of receiving acupuncture. There are inherent difficulties in the use of sham acupuncture as a control group. In future studies, other acupuncture points or alternative needling methods can be designed to form a more compatible control group for treating insomnia. Sometimes sample size determination is not easy when lacking related research data. According to the Central Limit Theorem, if the number of sampling case is 30 or more cases, the sampling distribution has an approximate normal distribution. It is recommended to have more than 30 participants in each group to ensure sufficient statistical power for a well-designed study.

Stilnox (Generic name-Zolpidem), which was used in this study is an effective hypnotics for patients with insomnia[11]. However, most of the withdrawn participants (43%) were concerned about the possible side effect due to continuous use of hypnotics and opted to drop out of the study. Compared with Groups A, Group B and Group C had a relatively lower withdrawal rate, indicating the demand of patients with insomnia for alternative approaches besides hypnotics. Consensus among experts offered guidelines that recommend the use of zolpidem on an "as-needed" or intermittent basis for patients with insomnia[12]. The PSQI also includes an item "use of sleeping medication" for assessing the outcome of treatments. More practical clinical trials can be designed allowing participants to use Stilnox

in "as-needed" regimens for further study.

According to the perspective of the meridian system in Traditional Chinese Medicine, insomnia is due to an imbalance in the Yin and Yang forces of the body. Insomnia is manifested in different patterns: deficiency in Qi of both the Heart and Spleen, disharmony between the Heart and Kidney, disturbance due to excess heat in the Liver, and dysfunction of the Stomach[13]. In order to cover all patterns of insomnia, eight acupuncture points were used bilaterally to restore the balance between the Yin and Yang forces through stimulation of different meridian points that govern different parts of the body and their interaction.

The small number of participants and high drop-out rate are the limitations of this study. However, it might reflect the fact that providing effective treatment for insomnia is still a continuing challenge. Since insomnia is a highly heterogeneous disease with different etiology and severity, acupuncture is likely to have different effects on different sub-groups of patients. Therefore, future clinical trials should focus on a particular sub-group or include a large sample size for distinguishing the effect of acupuncture on different types of patients.

Conclusions

The effectiveness of acupuncture alone or in combination with Stilnox remains uncertain, because of the small sample size and high drop-out rate, especially in the medication-only group. The results indicate that there is no evidence that acupuncture plus Stilnox is either better or worse than acupuncture alone; and there is insufficient data to compare acupuncture alone with Stilnox alone, or acupuncture plus Stilnox with Stilnox. The initial data may reveal potential beneficial effects of acupuncture in treating insomnia.

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針刺臨床試驗治療失眠症的經驗分享

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目的：1.針刺療法與西藥Stilnox（俗名-Zolpidem）治療失眠症的療效比較。2. 針刺療法與西藥Stilnox合併使用治療失眠症是否更具療效。方法：自2007年8月至2008年5月，以隨機對照試驗 (Randomized Controlled Trial, RCT)方式收案，在臺北市立聯合醫院中興院區進行臨床試驗。參加者被隨機分為A組 (每天睡前服用5毫克Stilnox)、B組 (每天睡前服用5毫克Stilnox，並每週接受針刺治療3次) 及C組 (未服藥，僅每週接受針刺治療3次) 三組。治療期間為4週，並於治療後4週，接受隨訪（follow up）。受試者治療前及每週治療後均接受匹茲堡睡眠品質量表（PSQI）的療效評估。**結果：**總共有48位參加臨床試驗，其中未完成療程即退出者有28人，完成療程及追訪之受試者共20人，包括A組2人，B組10人，C組8人。治療結果顯示，B組或C組受試者在接受針刺治療三週及四週後的PSQI分數，與治療前的PQSI分數作比較，在統計學上均具有顯著的差異存在（$P<0.05$），且在治療後四週追訪時，其療效然存在。而B組與C組兩組間，則無統計上顯著差異（$P=0.73$）。**結論：**本研究受限於樣本數太小及高退出率，單獨採用針刺療法或合併使用Stilnox治療失眠症的療效仍不確定，但初步資料顯示，利用針刺治療失眠症，可能有其潛在的效益存在。

關鍵字：失眠、匹茲堡睡眠品質量表（PSQI）、針刺

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