Effect of Zolpidem on Sleep Quality of Professional Firefighters; a Double Blind, Randomized, Placebo-Controlled Crossover Clinical Trial

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Abstract- Professional firefighting is among the most demanding jobs. Prior studies have showed the notable prevalence of poor sleep quality among professional firefighters that may result in catastrophes. The aim of this study was in field confirmation of zolpidem usage (10 mg/PO/bed time) for short term management of poor sleeps quality among professional firefighters. In a double-blind, randomized, placebo-controlled crossover clinical trial among professional firefighters, 27 poor sleepers were assigned randomly to one of the two groups. Two 14 days experimental periods were separated by a 14-day washout phase. Sleep quality was assessed using the Persian version of Pittsburgh Sleep Quality Index (PSQI). Six of the 27 enrolled voluntaries dropped out. Two rare side effects of zolpidem occurred in the study. A significant improvement of the PSQI score was detected in zolpidem period versus placebo in both groups (7.14 ± 3.02 *vs* 12.38 ± 2.51, $P<0.001$) although zolpidem had no significant effect on time of waking up (6.76 ± 1.21 vs. 6.64 ± 1.27, $P=0.89$). Zolpidem significantly improved all components of PSQI (Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances and Daytime dysfunction) in the current study except the use of sleep medication. Sleep onset latency was the component of PSQI with the greatest degree of abnormality among firefighters in a previous study. Interestingly, sleep latency was the component of PSQI with the most treatment effect of zolpidem in the current study. Zolpidem can be used as a part of treatment regimens in short time management of poor sleep quality among professional firefighters.

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Introduction

Professional firefighting is among the most physically and mentally demanding jobs, not only about fighting fire but also all manner of emergency situations such as traffic accident or hazardous spill. Prior researches have showed the notable prevalence of sleep disturbances and poor sleep quality among professional firefighters (1-3) that may result in weakened job performance and even catastrophes during stressful situations (4). Iranian firefighters generally work in a 24/48 schedule. They must do critical tasks when they are awake or upon sudden awakening from sleep, therefore they cannot use hypnotic/sedative medications to nap in firehouses or even afford their next day residual effect when administrated bedtime before work shifts (4).

Sleep promoting medications are useful in short term management of sleep problems, but performance decrement within next day of taking these drugs is an issue of concern, particularly in the situations that require continuous 24-hour operations. Zolpidem is one of the most commonly prescribed sleep pills worldwide (5). It is widely available in Iran, unlike the zaleplon, zopiclone, eszopiclone or ramelteon that their administration is not common except in very special cases. This non-benzodiazepine sedative-hypnotic agent have some advantages over the classic benzodiazepines especially with respect to rapid onset, short half-life, preservation of sleep architecture and lower risk of tolerance, dependence and abuse, particularly in low-

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dose and short-term prescription. Zolpidem acts via benzodiazepine type one receptors with less inducing sleep apnea compared with benzodiazepines. It is metabolized by cytochrome P450, and its metabolites are eliminated through urinary excretion (6-8).

Some previous studies showed a significant effect of zolpidem on sleep quality and even fatigue management of some employees (9). Clinical pharmacokinetic and pharmacodynamic characteristics of zolpidem, especially terminal elimination half-life of only 1.5 to 3.2 hour (10-11), suggest zolpidem as a theoretically ideal option for short term management of sleep problems among professional firefighters; but considering special features of this job, in field confirmation among them was required.

Materials and Methods

We designed this study as a randomized, double-blind, placebo controlled cross-over trial. Study participants were selected on the basis of poor sleep quality established by Pittsburgh sleep quality index (PSQI) from the database of another study on sleep quality of professional firefighters in Tehran (1); and all firefighters with the score more than five were eligible. Firefighters with any acute or chronic disease or medication usage that might interfere with sleep quality were excluded. Those who had a history of major life stressors (according to the Holmes and Rahe Stress Scale) one year or less prior to the study were excluded too.

According to the special design of the study, results of a similar study with zaleplon12 (PSQI was 11.7 ± 2.1 and 6.5 ± 2.8 before and after intervention, respectively) and considering 0.05 and 80% as the confidence level and power of the study, sample size was calculated to be at least 15.

A total of 27 voluntaries agreed to participate. After a comprehensive medical history and physical examination of voluntaries by an occupational medicine resident, they were informed of the aims and design of the study and signed written informed consent. Using STOP-BANG questionnaire, obstructive sleep apnea was not suspected among participants. The research protocol was approved by the ethics committee of Tehran University of Medical Sciences (No. 130/1253/D - 6 June 2011) and was registered with Iranian Registry of Clinical Trials (Trial acronym: IRCT201106076724N1).

Duration of this study was 6 weeks; two 14 days experimental periods were separated by a 14-day washout phase. The sequence of treatments (zolpidem-placebo or placebo-zolpidem) was determined randomly by a physician who was not in the research process and all study staff, and firefighters were blind for the sequence. Zolpidem and placebo were prepared in identical-looking packages. We used zolpidem HEXAL® (Zoldem®) 10mg in this study because of acceptability among many Iranian physicians and patients and ease of access in Iranian pharmaceutical market. We had no participant older than 60 years old. Each participant was given two containers with medication (A & B) and was instructed to take a pill bedtime except for night shifts, based on the plan that was given to him. A 24-hour hotline was determined for regular monitoring, any question, reporting adverse effects and emergency situations. Considering the characteristics of the intervention (10-11), at the beginning of the research and at the end of each experimental period, the PSQI and a data collection sheet for possible side effects of medications and participant's comments were completed (13).

PSQI is a widely used valuable instrument to measure the quality and patterns of sleep in both clinical practice and research activities (14). Good test-retest reliability and internal consistency (Cronbach's alpha = 0.82) of the Persian version have been showed before (15). This instrument distinguishes poor and good sleep by measuring seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. Scoring of answers is based on a 0 to 3 scale for each component, and 3 reflect the negative extreme on the Likert Scale. Total score or global PSQI score could be within a range of 0 to 21 and a global PSQI score > 5 indicates a poor sleep. Higher scores indicate worse sleep quality.

Two independence t-test, Mann-Whitney U test and *Chi*-square test were used to compare demographic features of two groups (zolpidem-placebo vs. placebo-zolpidem) and treatment effect, time effect and carry over effect according to Fleiss 198613 using SPSS 20. For all tests $P<0.05$ considered as the level of significance.

Results

Six of the 27 enrolled voluntaries dropped out; one firefighter without any reason (on placebo period) and second because of his sister recommendations who was a health care worker (on placebo period), both without any adverse effect or disturbance. A patient requested to leave the study because of experiencing an unusual and

unpleasant falling sense followed by "anesthesia like" sleep attack after the first time of taking zolpidem; according to the best of our knowledge, a never reported side effect of this drug (16-17). The next morning, he could remember that experience. Another participant's wife reported notable sleepwalking of her husband two consecutive nights of zolpidem usage while the participant had no memory of actually walking or even dreaming about. He had not any history of somnambulism, head trauma or medication usage, and we did not ask about alcohol or substance abuse. It is a less common adverse effect of this drug (16-17). He did not agree with our recommendation for a one-night polysomnography and we advised him to interrupt the study. Research team refused the study results of two participants because of very poor cooperation, the significant conflict between their oral and written reports and serious doubt on their performance regarding research protocol.

The statistical analysis, therefore, was carried out on 21 male patients. Tables 1 and 2 show demographic and baseline sleep characteristic of participants with a comparison between two groups. As seen in these tables, there is no significant difference between the two groups about above mentioned features that are ideal for analysis.

Table 1. Baseline demographic and sleep characteristics of participants with comparison between two groups (Numeric variables)

Sequence of interventions	ZP (n=11) Mean(±SD)	PZ (n=10) Mean(±SD)	*P*-value
Age (year)	35.55(±7.7)	35.30(±9.7)	0.949*
Job Experience (year)	11.86(±5.43)	12.80(±6. 13)	0.819*
Number of children	1(±0.49)	1.29(±0.56)	0.517*
Cigarette per day	2.82(±1.21)	0.5(±0.28)	0.512+
Cup of Tea per day	7.09(±3.06)	5.7(±2.68)	0.809+
Cup of Coffee per day	0. 90(±0.30)	0.51(±0.21)	0.223+
C1†	2.36(±0.505)	2.08(±0.422)	0.099+
C2†	2.64(±0.674)	2.60(±0.516)	0.756+
C3†	1.91(±1.04)	1.80(±1.13)	0.863+
C4†	1.18(±0.48)	1.20(±0.53)	0.973+
C5†	1.73(±0.79)	1.60(±0.699)	0.099+
C6†	0(±0)	0(±0.0)	1+
C7†	2.36(±1.07)	2.90(±0.316)	0.282+
PSQI‡	12.18(±2.60)	12.9(±2.23)	0.508*

ZP: zolpidem-placebo sequence, PZ: placebo-zolpidem sequence
*:P value with use of two independence t-test,
+: P-value with use of Mann-Whitney U test
†The components of PSQI
‡The global score of PSQI

Table 2. Baseline demographic characteristics of participants with comparison between two groups (Qualitative variables)

Sequence of interventions	ZP (n=11) N (%)	PZ (n=10) N (%)	*P*-value*
Marriage status (Married)	10(90.9%)	7(70.0%)	0.311
Education (more than diploma)	5(45.5%)	3(30.0%)	0.659
Having second job (yes)	6(54.5%)	4(40.0%)	0.670

ZP: zolpidem-placebo sequence, PZ: placebo-zolpidem sequence,
*:P value with use of *Chi*-Square *t-t*ests

Mean ± SD of baseline PSQI score was 12.52 ± 2.40 among participants which were compatible with very poor sleep quality. A significant improvement of the PSQI score was detected in zolpidem period versus placebo in both groups (7.14 ± 3.02 *vs.* 12.38 ± 2.51, $P<$ 0.001). Table 3 shows treatment effect, time effect and carry over effect for a global score of PSQI. The treatment effect of zolpidem is visible in Figure 1 too.

Treatment, time and carry over effect were also determined for components of PSQI. The treatment effect of zolpidem on these components is shown in Table 4. Time effect and carry over effect on the components were not statistically significant. Figure 2 compares treatment effect of zolpidem on components of PSQI.

Mean ± SD of "Time of going to bed", "Subjective Sleep onset latency" and "Time of waking up" were 23.76± 1.11(hour), 45.48 ± 14.74(min) and 6.57±1.42 (hour), respectively. Zolpidem reduced subjective sleep

onset latency versus placebo (17.86 ± 8.29 (min) vs 49.29 ± 22.06 (min), *P*<0.001) but had no significant effect on time of going to bed (23.35 ± 0.77 vs 23.42 ± 0.88, *P*=0.44) and time of waking up (6.76 ± 1.21 *vs.* 6.64 ± 1.27, *P*=0.89).

Table 3. Test of Treatment, Time, and Carry over effect estimation for global score of PSQI variable

	Mean (±SD) 95% CI for ZP		*P*-value
Treatment effect	-5.21(± 0.6) (-6.23 , -3.97)		<0.001*
Sequence of interventions	**ZP**	**PZ**	
Time effect Mean(±SD)	2.82(±1.57)	2.4(±1.10)	0.493*
Carry over effect Mean(±SD)	9.45(±2.21)	10.1(±2.7)	0.557*

ZP: zolpidem-placebo sequence
PZ: placebo-zolpidem sequence
*:P value with use of two independence *t*-test
+: P-value with use of Mann-Whitney U test

Table 4. Treatment effect of Zolpidem on components of PSQI

components of the PSQI	Before intervention (Zolpidem) Mean ± SD	After intervention (Zolpidem) Mean ± SD	Treatment effect (Z-P) Mean ± SD 95% CI for ZP	*P*-value
Subjective sleep quality (C1)	2.57 ± 0.50	1.38 ± 0.68	- 1.03 ± 0.19 (-1.43 , -0.64)	<0.001*
Sleep onset latency (C2)	2.62 ± 0.59	0.76 ± 0.06	- 1.71 ± 0.17 (-2.08 , -1.35)	<0.001*
Sleep duration (C3)	1.86 ± 0.86	1.14 ± 0.55	- 0.57 ± 0.15 (-0.88 , -0.25)	0.004+
Habitual sleep efficiency (C4)	1.19 ± 0.43	0.57 ± 0.08	- 0.79 ± 0.16 (-1.14 , -0.44)	<0.001*
Sleep disturbances (C5)	1.67 ± 0.73	1.29 ± 0.46	- 0.73 ± 0.14 (-1.01 , -0.44)	<0.001*
Use of sleep medications (C6)	0	0	- 0.05± 0.08 (-0.22 , 0.11)	0.314+
Daytime dysfunction (C7)	2.62 ± 0.80	2.00 ± 0.77	- 0.58 ± 0.13 (-0.85 , -0.30)	0.002+

Z-P: Zolpidem – Placebo sequence
*:P value with use of two independence *t*-test
+: P-value with use of Mann-Whitney U test

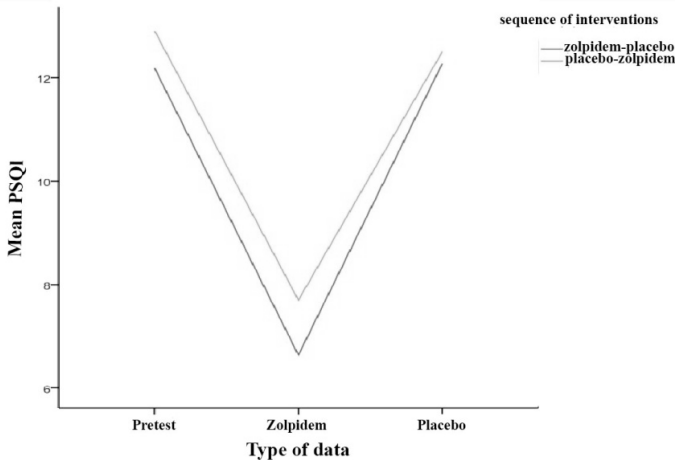

Figure 1. Treatment effect of Zolpidem

Discussion

Firefighting requires complex psychomotor abilities that may be impaired by sleep problems as well as sleep pills (4). Although the main treatment of the most sleep problems is a correction of underlying causes but in some cases, short-term prescribing of sleep medications as reinforcement for educational and behavioral techniques is inevitable (4).

Many past studies have shown high prevalence of poor sleep quality among professional firefighters (1-3) but impairment of psychomotor performance and increase the risk of work accidents are the most challenges of sleep medication usage among them and some other safety-sensitive employees.

The results of the current study indicated the notable effect of zolpidem on improvement of sleep quality among firefighters although the PSQI score remained slightly higher than normal after treatment. Nowadays, prescription of longer acting benzodiazepines has been abandoned except in some specific diseases (12, 18-19). They have a greater effect than short acting ones on next day residual effects and function including an increase the risk of motor vehicle accidents. About short-acting, tolerance, dependency and withdrawal syndrome are an issue of concern (12, 18-19). Zolpidem, as a short life non-benzodiazepine agent, is a suitable alternative. For example in another safety-sensitive occupation, professional drivers must be prohibited from commercial driving when requiring hypnotic medications but shorter acting hypnotics with half-lives of less than 5 hours for less than two weeks may permit driving under close medical supervision (19).

Current findings confirm the efficient therapeutic effect of zolpidem in treating uncomplicated and primary poor sleep quality of professional firefighters at least in short term period. Another study among military personnel working in irregular rotating shifts showed the opportunity to self-administer zolpidem in order to facilitate sleep, and the majority of them chose to take (9).

Although zaleplon, another non-benzodiazepine agent, has a shorter half-life and a shorter time to peak concentration compared to zolpidem that make it theoretically as a better choice in our setting (10-11,20), but in contrast to zolpidem, it is not easily available at a low price in Iranian pharmaceutical market now. A recently published article showed no significant differences between zaleplon and zolpidem in shortening of sleep onset latency (10).

Zolpidem significantly improved all components of PSQI (Subjective sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances and Daytime dysfunction) in this study except "use of sleep medication". A previous study has shown the therapeutic effect of zolpidem in subjective sleep quality and even next day performance among simulated night shift workers (21).

Zolpidem slightly reduced "time of going to bed" but had no significant effect on "time of waking up", these findings are congruent with data from other researches that assessed no residual effects seven hours after zolpidem usage (22-23). Another research found that zolpidem decreases self-reported sleep onset latency and increases night time sleep without any physical or psychomotor disturbance of performance on the fallowing day among healthy athletes (24).

Sleep onset latency was the component of PSQI with the greatest degree of abnormality among firefighters in a previous study (1). Interestingly, sleep latency was the component of PSQI with the most treatment effect of zolpidem in the current study that is compatible with zolpidem characteristics (6-7).

We recommend future studies to assess zolpidem effects at the lower dose (5 mg/PO/bed time) and zaleplon effect on sleep quality of professional firefighters with objective measurement of psychomotor performance on the fallowing day of usage.

The partially low number of participants and using a subjective instrument for sleep quality and daytime dysfunction evaluation of them, mainly due to restrictions on financial sources and poor administrative cooperation are the most limitations of this research. Notable dropouts (22%) are another limitation that was ethically inevitable, although this issue was considered in the analysis of the data. Despite the double-blind nature of the study, all voluntaries could easily distinguish between zolpidem and placebo periods of study by significant sleep prompting effects of zolpidem and report it, which was inevitable too.

Zolpidem can be used as a part of treatment regimens in short time management of poor sleep quality among professional firefighters. Where possible, simultaneous correction of the underlying causes under close supervision of sleep medicine experts may be helpful.

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