Comparative premedication efficacy of gabapentin, melatonin, and dextromethorphan in postoperative pain management following general anesthesia in hip fracture surgery: a randomized clinical trial

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Background
The effectiveness of postoperative pain relief regimens is well established and postulated to rely on diverse factors.
Objective
The aim of this study was to compare the effect of gabapentin and melatonin and dextromethorphan on postoperative pain control in patients undergoing hip fracture surgery under general anesthesia.
Patients and methods
In a double-blind controlled trial 125 patients requiring hip fracture surgery enrollment into the study after following ethical approval and informed participant consent. The patients were randomized to either each of the three regimens (gabapentin, melatonin, and dextromethorphan) by the block-randomization method. Outcome measurements were of foremost importance, patient's pain scores throughout the recovery time and scheduled postoperative time intervals (2, 4, 6, 12, 24 h), doses of opioid use (mg) in the initial 24 h, and at length, sedation levels using the Ramsay scoring system at the early postoperative time intervals. Moreover, complications including chills, nausea, vomiting, and decreased consciousness were recorded. Statistical data analysis conducted by analysis of variance, χ^2, and repeated measurements through SPSS, version 20.
Results
Gabapentin-treated patients manifested the lowest blood pressures ($P<0.05$), with maximum pain relief being experienced, sedation level being greater ($P<0.05$), and opioid use being lower in the group ($P=0.0001$).
Conclusion
We have the impression that gabapentin could be connected with improving pain relief and sedation, whereas opioid use was observed comparatively lower in the initial 24 h, and hence inferentially. The premedication can be driven to be superior in creating favorable conditions for analgesia and sedation and effective in preventing complications requiring treatment within 24 h postoperatively versus baseline and promisingly suggested to be continued for postoperative pain management, procedural sedation quality improvement, and opioid use reduction within the initial 24 h.

Keywords:
dextromethorphan, gabapentin, hip fracture, melatonin, pain management

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Introduction

The effectiveness of postoperative pain relief regimens is well established and postulated to rely on diverse factors covering the mental status, patient type of personality, consumption or nonconsumption of alcohol and drugs before surgery, age, and surgery type [1,2]. The multimodal combination of ketamine analgesia was corroborated to be novel and potential for postoperative pain improvement and complication reduction [3]. Notwithstanding currently it being the most effective in managing intraoperative and postoperative pain relief, the use of opioids may be coupled with side effects limiting their use, chiefly drowsiness, apnea, nausea, and vomiting [1,2,4]. Since a smaller dose of premedication needed to be frequently administered to reduce these side effects is not able to properly provide adequate pain management; growing attention was directed toward other drugs capable of being employed along with

opioids (not as a substitute) to help improve pain relief, whose adjuvant effect will cause a smaller dose of opioids to suffice to provide pain relief, with minimal side effects [4].

Among various effective premedication agents [1,5], gabapentin is believed to be a third-generation antiepileptic drug structurally similar to γ-aminobutyric acid, and pharmacologically described as [1-Aminomethyl]-cyclohexaneacetic acid [6,7]. Melatonin (N-acetyl-5-methoxytryptamine) is a hormone naturally produced in the brain, secreted by the pineal gland [8], whose receptors are found to be present in various areas of the brain and different tissues throughout the body, as reported in earlier studies [9]. The melatonin hormone is effective in combating sleep disorders, anxiety, and pain [8,9]. Melatonin has also anti-inflammatory and antioxidant properties, hence used as a premedication, and interacts with many receptor sites including opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α1-adrenergic and α2-adrenergic, and melatonergic receptors present in the dorsal horn of the spinal cord as well in the central nervous system [10,11]. Melatonin premedication reduces the need to request anesthesia intraoperatively. Different doses are used as a premedication for sedation and analgesia, without cognitive impairment and psychomotor skills and without increasing the recovery time [11,12]. Several studies besides mentioned the reduced pain caused by melatonin [11,13,14]. A review study (Anderson *et al.* 2014) [15] involving 24 clinical trials with 1749 participants showed that melatonin reduces anxiety and pain compared with placebo, where three studies explored the induction dose of anesthetics showing that melatonin reduced the dose of anesthetic but sevoflurane had no such effect [12]. Likewise, another study Norouzi *et al.* [16] concluded that melatonin premedication reduced propofol induction dose and those receiving melatonin had higher anxiety and sedation than placebo.

Dextromethorphan is an N-methyl-D-aspartate receptor antagonist, associated with improved postoperative pain relief, cheaper cost than opioids, and fewer side effects, including nausea and vomiting, drowsiness, and abdominal pain [17,18]. The effects of dextromethorphan is demonstrated on improving postoperative pain, in which dextromethorphan was used orally or through infusion at various doses of between 30 and 200 mg at different times (preoperative to 2 days postoperative), as well as the level of pain relief was determined compared with placebo or other analgesics such as NSAIDs [19]. As King *et al.* [20] stated, preoperative dextromethorphan can reduce opioid use in 24–48 h postoperatively and improve postoperative pain relief at 1, 4–6, and 24 h. Similarly, three trial studies [19,21,22] reported the same results on the relationship between dextromethorphan and pain.

Considering that some literature [11,13,14] tried to compare the effect of gabapentin and melatonin on postoperative pain management in various surgeries, however, no comparative study was hitherto performed on the efficacy of gabapentin, melatonin, and dextromethorphan in pain management after hip fracture surgery (HFS). Moreover, as the pain management is highly important in these patients, we decided to launch a study aimed at exploring the effect of oral gabapentin and melatonin and dextromethorphan on postoperative pain control in participants undergoing HFS under general anesthesia.

Patients and methods

Study setting

This study was a double-blind clinical trial in which 120 patients scheduled for were studied, following institutional approval and informed participant consent. Sample size calculation was conducted by considering study power 80%, confidence interval 95%, and pain score difference between intervention and placebo group in recent studies.

Ethical consideration

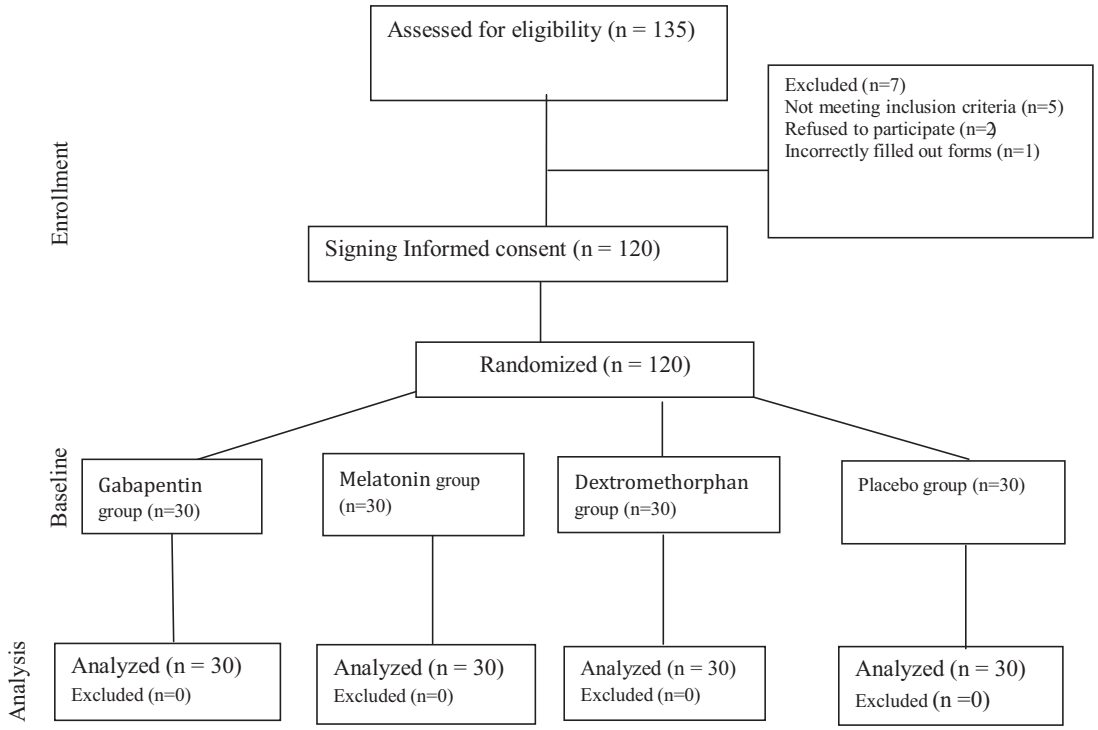
The study protocol is approved by the research ethics committee of medical university by IR.ARAKMU.REC.1398.286 code. Moreover, it is registered in Iranian Registry of Clinical Trials by IRCT20141209020258N136 clinical trial code.

Inclusion criteria were HFS patients, 17–65 years old, of both genders, lack of fractures in other limbs, no coagulation disorders, no history of cardiovascular, hepatic, or renal disease, no history of opioid use within the last 48 h, no history of drug/psychedelic substances/alcohol abuse. Exclusion criteria were reluctance to participate in the study and severe hemodynamic instability.

Intervention

The patients were split into four groups using block randomization as shown in Fig. 1. Group 1 received 6 mg melatonin (3 mg sublingual tablets; Webber Naturals, British Columbia, Canada) [23]; group 2

Figure 1



Consort diagram showing the flow of participants through each stage of a randomized trial.

received1 mg/kg oral dextromethorphan (15 mg scored tablets; Pursina Pharmaceutical Co., Iran); group 3 received 600 mg of gabapentin (Gabafort 600 mg tablets; Tehran Chemie Pharmaceutical Co., Iran); and group 4 received the same amount of distilled water (all at 90 min) orally preoperatively. The first three drugs were dissolved in water to a final volume of 5 ml. It is noteworthy that to ensure a double-blind study, the intern was unaware of the drugs prescribed in each group, the anesthesiologist who prepared the drugs did not provide them with the intern, and besides the participants were not aware of their allocation.

All participants were hospitalized for at least one day preoperatively and kept nil per os for 8 h. Basic information about heart rate, mean arterial pressure measured by noninvasive monitoring, and arterial oxygen saturation were gathered and recorded preoperatively, every 15 min until the end of surgery, and during recovery.

In all patients, 10 ml/kg of crystalloid Ringer's solution was administered in the supine position on arrival to the operating room. Then, all received general anesthesia with 5 mg/kg thiopental sodium, 1.5 μg/kg fentanyl, and 0.5 mg/kg atracurium and then were intubated with a proper-cuffed endotracheal tube size. Every half hour, anesthesia was maintained with oxygen and nitrous oxide (50 : 50) and isoflurane 1%, as well as intravenous fentanyl and atracurium were infused at a dosage of 50 μg and 10 mg, respectively. The postoperative pain scores based on a visual analog scale for all four groups were evaluated using a ruler graded from 0 to 10, at the time of recovery and at 2, 4, 6, 12, and 24 h. If the participant had a visual analog scale more than 4, 50 mg of intramuscular meperidine was administered, the time was recorded, and then opioid use (mg) in the first 24 h was noted.

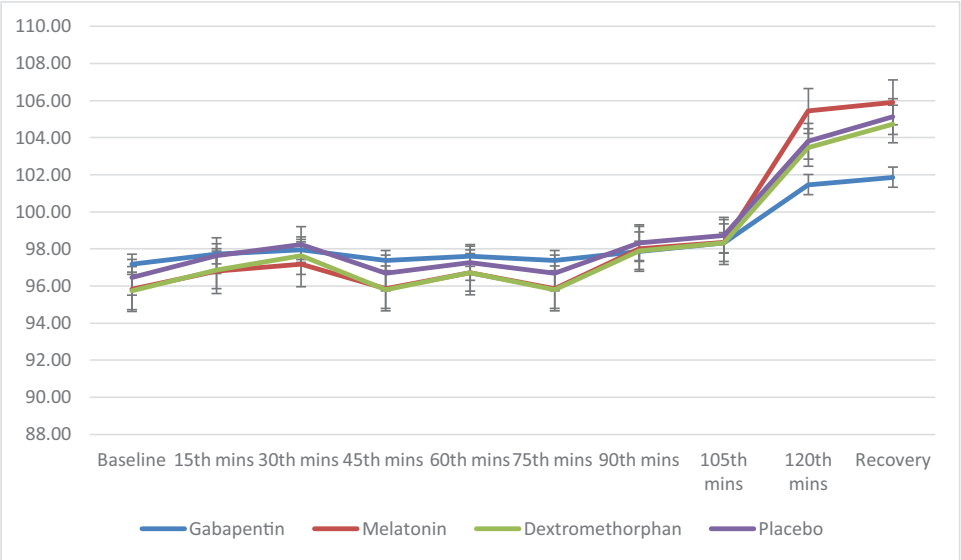
Measurements and statistical analysis

We gathered sedation levels using the Ramsay scoring system at 2, 4, 6, 12, and 24 h postoperatively and controlled patient's complications, for instance, supplemental oxygen therapy for hypoxia (saturation oxygen<92%), as well as administration of crystalloid serum and, if needed, sympathomimetic administration for hypotension (blood pressure<20% from baseline), if happened. Furthermore, bradycardia (heart rate<40) was controlled with atropine 0.5 mg intravenously, while recording any other complications, if happened, and taking remedial action. In case of chills, nausea, vomiting, and decreased consciousness, we recorded the complications.

Statistical analysis

Statistical data analysis was conducted by analysis of variance to compare hemodynamic parameters in four

Figure 2



Comparison of the trend mean of blood pressure in the groups at different times after beginning surgery.

Table 1 Comparison of the mean and SD of pain score in the groups

Pain score	Gabapentin (mean ±SD)	Melatonin (mean ±SD)	Dextromethorphan (mean ±SD)	Placebo (mean ±SD)	*P* valuea
Recovery	1.13±0.35	1.27±0.45	1.33±0.48	1.50±0.51	0.019
2 h. after the beginning of surgery	2.13±0.35	2.27±0.45	2.33±0.48	2.50±0.51	0.019
4 h after the beginning of surgery	3.07±0.25	3.13±0.35	3.20±0.41	3.37±0.49	0.021
6 h after the beginning of surgery	3.93±0.45	4.13±0.35	4.17±0.38	4.33±0.48	0.004
12 h after the beginning of surgery	4.37±0.49	4.63±0.49	4.63±0.49	4.73±0.45	0.026
24 h after the beginning of surgery	5.23±0.63	5.47±0.57	5.23±0.43	5.57±0.50	0.036

[a]Based on analysis of variance tests.

groups. χ^2 test was used to compare sex distribution and incidence of consequences among groups. Analysis of variance for repeated measurement tests were used to compare the between-group differences between hemodynamic parameters [24]. All analyses were conducted through SPSS version 20 (SPSS Inc., Chicago, IL, USA).

Results and discussion

Our results showed that the minimum age was 20 years and the maximum was 69 years. The mean age was 39.53±11.10 years and 64 (53.3%) and 56 (46.7%) participants were male and female, respectively. No statistical significance was found among the groups in terms of age, sex, mean oxygen saturation, heart rate, and duration of surgery ($P<0.05$).

On the basis of the results (Fig. 2), statistically significant differences were observed in blood pressure among the four groups, only at 120 min after the beginning of surgery ($P=0.029$) and recovery ($P=0.005$), but in another times there was no significant difference ($P>0.05$). Though blood pressure was lower in the gabapentin group, no statistically significant difference was observed among the groups in terms of blood pressure, according to the repeated measures test ($P>0.05$).

Table 1 shows that statistically significant differences were seen among the groups, based on the results of pain score ($P<0.05$). These results show a lower score in the gabapentin group than in the other groups. On the basis of repeated measures test, statistically significant differences were also observed among the groups in terms of pain ($P<0.05$). It was lower in the gabapentin group than in the other groups.

According to the results in Table 2, statistically significant differences were seen among the groups

Table 2 Comparison of the mean and SD of sedation score in the groups

Sedation score	Gabapentin (mean ±SD)	Melatonin (mean ±SD)	Dextromethorphan (mean ±SD)	Placebo (mean ±SD)	*P* valuea
Recovery	2.53±0.51	2.53±0.51	2.53±0.51	2.00±0.91	0.002
2 h after the beginning of surgery	2.10±0.31	2.10±0.31	2.13±0.35	1.80±0.61	0.006
4 h after the beginning of surgery	2.00±0.00	2.00±0.00	2.00±0.00	1.77±0.43	<0.001
6 h after the beginning of surgery	1.93±0.25	1.87±0.35	1.80±0.41	1.33±0.48	<0.001
12 h after the beginning of surgery	1.63±0.49	1.37±0.49	1.37±0.49	1.20±0.41	0.006
24 h after the beginning of surgery	1.10±0.31	1.00±0.00	1.00±0.00	1.00±0.00	0.025

[a]Based on analysis of variances test.

Table 3 Comparison of the mean and SD of opioid use in the groups

Variables	Groups				*P* value
	Gabapentin (mean ±SD)	Melatonin (mean ±SD)	Dextromethorphan (mean ±SD)	Placebo (mean ±SD)	
Opioid use within 24 h	66.66±23.97	88.33±21.51	90.0±20.34	106.66±17.28	<0.001a
Consequences [*n* (%)]	0	0	3 (10)	0	0.026b

[a]Based on analysis of variance tests. [b]Based on χ^2 test.

in terms of the sedation score, based on repeated measures test ($P<0.05$). Sedation score was greater in the gabapentin group than in the other groups. As depicted in Table 3, statistically significant differences were found among the groups in terms of opioid use, as shown in the above results ($P<0.001$), whereas the gabapentin group was lower in opioid use. Moreover, the complications and consequences were higher in the dextromethorphan group ($P=0.026$).

According to this double-blind clinical trial, no statistical significance was found among the groups in terms of mean oxygen saturation, heart rate, and duration of surgery, but the blood pressure and pain scores were statistically significant and were lower in the group receiving gabapentin. In addition, sedation quality was better in the group and opioid use was lower in the gabapentin group than in the other groups. Overall, gabapentin reduces pain and increases sedation, whereas opioid use was lower in the gabapentin group within 24 h. A systematic review showed that taking preoperative gabapentin helped significantly improve postoperative pain relief compared with the control group and could also reduce the dose of opioids and reduce their side effects [25].

Gabapentin works as the most important neurotransmitter in the brain, and is pharmacologically described as [1-Aminomethyl]-cyclohexaneacetic acid [23]. Gabapentin has a half-life of 5–6 h, does not change, and is mainly excreted in the urine [7,23]. Besides treating epilepsy, it has been found useful for disorders such as neuropathic pain, psychiatric diseases, movement disorders, alcohol dependence, and restless leg syndrome. In addition, gabapentin has also been widely used in treating diabetic neuropathy and inflammatory pain and in alleviating postoperative pains [26]. Gabapentin does not interfere with other widely used drugs and has been deemed a remarkable drug, due to its low cost, high availability, and minimal side effects. It acts by binding to the alpha-2-delta subunit of voltage-dependent calcium channels, decreases the release of excitatory neurotransmitters, and ultimately improves pain relief and reduces central pain perception [26,27].

Modir *et al.* [28] recently undertook a randomized clinical trial aimed at the preventive effect of oral caffeine and melatonin on headache after spinal anesthesia for lower limb surgery and suggested that both caffeine and melatonin improved pain relief without any adverse hemodynamic changes. In our study, melatonin besides provided sedation and pain relief, but the effect of gabapentin was greater. The Javaherforooshzadeh *et al.* [13] study (2018) addressed comparing the effect of melatonin and gabapentin on postoperative anxiety and pain in lumbar spine surgery and concluded that both were effective in reducing

pain. These results were in line with those of ours. The Khalili *et al* [29] study that aimed at oral gabapentin and intravenous paracetamol in tibial fracture surgery suggested that both had a similar effect on improvement in postoperative pain relief without any side effects [29], whereas our results showed improved pain relief and increased sedation in the gabapentin group.

King and colleagues conducted their review of the effect of dextromethorphan on postoperative pain relief and demonstrated that preoperative dextromethorphan helps reduce opioid use in 24–48 h postoperatively and improve pain relief at 1, 4–6, and 24 h postoperatively, while though dextromethorphan in our study was effective, gabapentin efficacy was greater. A study by Khalili *et al.* [30] evaluating the effect of gabapentin and diclofenac on postoperative pain suggested that they could help manage postoperative pain, whose results were consistent with our study. An evaluation of the efficacy of melatonin, clonidine, and gabapentin in reducing anxiety and pain in patients undergoing cholecystectomy [14] demonstrated that the use of melatonin has an efficacy similar to that of clonidine and gabapentin in reducing preoperative anxiety, improving postoperative pain relief, and reducing opioid use.

Gabapentin in our study is associated with improved pain relief, greater sedation, and lower opioid use within 24 h. The results of the Entezary *et al* [22] study exploring the effects of oral dextromethorphan on preoperative pain relief after knee arthroscopy showed that preemptive use of dextromethorphan can improve postoperative pain relief and reduce postoperative opioid use. Though this was also effective in our study, gabapentin had more efficacy. Khezri and Merate [11] evaluated the effect of melatonin and gabapentin on anxiety and pain after cataract surgery and concluded that the level of anxiety was significantly lower in both intervention groups than in the placebo one. In addition, gabapentin improved pain relief and sedation scores during retrobulbar placement compared with placebo.

Their results were consistent with those of ours. Mirzae *et al.* [31] undertook a study comparing the effect of gabapentin on postoperative pain relief using intrathecal fentanyl. Despite the traditional use and reliable analgesia of fentanyl, gabapentin can be used as a viable alternative, mainly in opioid contraindications. Their results were consistent with our study.

Another study, aimed to assess the effect of melatonin as a premedication on laparoscopic cholecystectomy; the lowest level of anxiety was in the midazolam group, but no statistical difference was observed between the two groups, while it was significantly higher in the placebo group. Furthermore, sedation was lower in the melatonin group when compared with midazolam. They concluded that melatonin could be used successfully as a premedication in cholecystectomy [32]. Furthermore, the Norouzi *et al.* [16] study suggested that melatonin premedication reduced propofol induction dose, whereas those receiving melatonin had higher anxiety and sedation than placebo. Melatonin in our study was more effective than placebo, but gabapentin efficacy was better. The Manochehrian *et al.* [33] study showed that preoperative oral administration of 90 mg of dextromethorphan could improve postoperative pain relief after ligation surgery, mainly in recovery, 2 and 4 h postoperatively. Nevertheless, gabapentin and dextromethorphan were more effective in our study. Mousavi Buiki and Movafegh [19] undertook their study on the effect of dextromethorphan on pain intensity after open gallbladder surgery, based on which dextromethorphan can be used in combination with opioids and other analgesics to improve postoperative pain relief. A similar result was found in our study, but gabapentin was further effective. The Wadhwa *et al.* [34] study assessed the effect of large-dose oral dextromethorphan (200 mg every 8 h) in reducing pain after knee surgery and concluded that increasing orally administered dextromethorphan to near-maximum tolerable dose did not significantly reduce the morphine required. In addition, dextromethorphan cannot improve pain relief as expected from N-methyl-D-aspartate antagonist drugs, while being effective in ours, but gabapentin was more effective.

Conclusion

Overall, gabapentin could improve pain relief and increase sedation, whereas opioid use was lower in the first 24 h, hence as one may infer, the premedication can be driven to be superior in creating favorable conditions for analgesia and sedation. Moreover, it is effective in preventing complications requiring treatment within 24 h postoperatively versus baseline and promisingly suggested for postoperative pain management, procedural sedation quality improvement, and opioid use reduction within the first 24 h.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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