DISCUSSION

Shivering is a frequent challenge to anesthetists as it increases discomfort of the patients and surgeons, It interferes with monitoring of electrocardiogram, blood pressure and oxygen saturation. In addition, it increases oxygen consumption, carbon dioxide production and lactic acidosis, also it increases metabolic heat production up to 500-600% above base level and increases the operative pain by stretching the surgical incision, increase the intraocular pressure and the intracranial pressure. Moreover, it is blamed for hemodynamic changes and increases in heart rate and cardiac output; and thus, it may cause distress to patients especially those with low cardiopulmonary reserve.

Shivering, which occurs usually as a thermoregulatory response to cold, may also occur following general or neuraxial anesthesia.Unfortunately, controlling patient's core temperature with warm I.V. fluids and ambient temperature does not always prevent shivering, Evidences suggested that opioid kappa-receptor plays an important role in modulation of postoperative shivering and this explains the greater efficacy of pethidine compared with equi-analgesic doses of opioid mu-receptor agonists such as morphine, fentanyl, alfentanil and sufentanil. Although pethidine, in the doses effective in treating post-anesthetic shivering (0.33– 0.4 mg/kg), rarely produces cardiovascular effects, it may potentially cause respiratory depression, especially if it or other opioids have been given intraoperatively as analgesia, so other drugs were investigated for their efficacy as anti-shivering agents as tramadol and granisetron which were tested in this study for their efficacy to control post-spinal anesthesia shivering.

The current study was carried out to compare the efficacy of tramadol versus granisetron in order to treat shivering in patients undergoing elective orthopedic surgeries under spinal anesthesia.

It was carried out in the Orthopedic Unit, in El Hadara University Hospital, on 60 patients, aged 18-40 years old, ASA I-II, scheduled for elective orthopedic procedures under spinal anesthesia, after the approval from the Local Ethical Committee and informed written consents from all the patients in the study.

Patients were randomly assigned (double-blind, closed-envelope randomization) into two equal groups (30 patients each) according to the drug administred:

Group T : Tramadol 1mg/kg

Group G : Granisetron 40 μg/kg

As regards changes in heart rate, there was no significant difference between the two study groups in the time period immediately before spinal anesthesia.

In group T, after the spinal anesthesia, the fifteen alternative time of follow up showed a significant decrease in heart rate. This could be explained by its endogenous opioid activity through both low binding affinity of the parent compound and higher binding affinity of the O-demethylated metabolite (M1) to μ-opioid receptors.[97]

In group G, after the spinal anesthesia, the fifteen alternative time of follow up showed a significant increase in heart rate. This could be explained by its 5-HT_3 receptor antagonistic properties.[98]

Lesser et al. mentioned that risk factors for bradycardia and asystole during neuraxial anesthesia include low baseline heart rate, first degree heart block, high sensory level, male gender and β blockers, he concluded that moderate to severe bradycardia can occur at any time during neuraxial anesthesia regardless of the duration of anesthesia and that low baseline heart rate increases the risk of bradycardia.[99]

However, in the present study the changes in heart rate were mainly attributed to the effect of tramadol and granisetron rather that of spinal anesthesia.

In the present study, the mean arterial blood pressure (MABP) of the patients in the two study groups showed no significant statistical differences immedaitely before spinal anesthesia. However, fifteen minutes after spinal anesthesia, there was a significant decrease in the MABP, after that from the 30 minutes interval until the of the study, there was no statistical significant difference between the two groups. The decrease in the MABP in the 15 minutes interval might be explained by the spinal block-induced sympathectomy. Hypotension occurs as result of block of vasomotor tone which is primarily determined by sympathetic fibers arising from T5 to L1 innervating arterial and venous smooth muscles. Blocking of these nerves causes vasodilatation of the venous capacitance vessels, pooling of blood, and decreased venous return to the heart. [100]

Nagan et al. mentioned that preloading allows for the compensation of any preoperative fluid deficit, as well as, compensating for the dilatation of the venous system. The main beneficial effect of administration of intravenous fluids was to increase cardiac output and this subsequently will correct hypotension.[101]

Kyokong et al investigated the incidence and risk factors of hypotension and/or bradycardia in patients receiving spinal anesthesia and concluded that the incidence of hypotension and bradycardia may increase with increasing age or analgesic level up to T4 dermatome or higher, also there are three other risk factors may be responsible for hypotension after spinal anesthesia which are: prehydration fluid of less than 500 ml, caesarean section and body mass index of 30 or more.[102]

However, Rout et al. found that hypotension associated with spinal anesthesia for cesarean section cannot be eliminated by volume preloading and that the requirement for a mandatory administration of a fixed volume before spinal anesthesia for urgent cases should be abandoned.[103]

To conclude, the changes in the mean arterial blood pressure in the study groups was mainly attributed to the effects of spinal anesthesia not due to the studied drugs.

In the present study, on comparing the two studied groups, it was found that there was no statistical significant difference between the two studied groups regarding core temperature immediately before intrathecal injection, then there was statistical significant decrease regarding the core temperature in the tramadol group than the granisetron group. Temperature readings ranged between 35.77-36.35 ºC in the tramadol group and they ranged between 36.46-36.84 in the granisetron group. This might be explained by the fact

that tramadol slightly inhibit thermoregulation [104], while granisetron group did not show significant difference regarding the core temperature and this may be due to the influence of 5-hydroxytryptamine receptor on both production and heat loss pathways [105]

In the current study, the recurence of shivering was investigated in the two groups of study and it showed that the incidence of recurrence of shivering was 10% in the tramadol group, while it was 30% in the granisetron group.

According to shivering severity; in the tramadol group, 10% of patients experienced shivering grade (1) and 0% experienced grades (2,3 & 4); whereas in the granisetron group, 16.67% of patients experienced shivering grade (1), 6.67% experienced shivering grade (2) and 6.67% experienced shivering grade (3). Therefore, shivering severity was clearly lower in patients who used tramadol than those who used granisetron.

This decrease in the incidence of shivering with the patients receiving tramadol can be attributed to the fact that it is a NMDA receptor antagonist. these receptors have important role in the thermoregulatory mechanisms and they are distributed in various sites in both the brain and spinal cord. NMDA receptor agonists increase the firing rate of neurons in the preoptic anterior hypothalamus and modulate noradrenergic and serotoninergic neurons in NMDA receptors in the locus coeruleus. Also, NMDA receptors at the dorsal horn of spinal cord modulate ascending nociceptive transmission. NMDA receptor antagonists modulate shivering by interfering with the central thermoregulatory control mechanism. [106]

In addition to being a competitive NMDA receptor antagonist, tramadol is a norepinephrine reuptake inhibitor. Therefore it probably controls shivering by non-shivering thermogenesis by the beta-adrenergic effect of norepinephrine. [107]

Ketamine which is a NMDA receptor antagonist has been proven to be an effective antishivering agent by many studies as follows:

Sharma et al reported that ketamine 0.5 mg/kg IV was effective for the treatment of postoperative shivering. However, this study was not double-blind and it had no positive control. [108] also, Emine et al compared the efficacy of IV ketamine 0.5 mg/kg, IV ketamine 0.75 mg/kg with IV pethidine 25 mg for the treatment of postoperative shivering after general anesthesia and reported that ketamine had a more rapid onset than pethidine for treating postoperative shivering during the initial 4 min after administration. The authors recommended that lower doses of ketamine needed to be investigated to determine the optimal dose of ketamine for the treatment of postoperative shivering. [109] Honarmand et al compared the efficacy of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anesthesia. The incidence of shivering in the four groups; control, midazolam, ketamine, and midazolam-plus-ketamine was 60%, 50%, 23.3%, and 3.3% respectively. [110] also, Kinoshita et al showed that during spinal anesthesia, infusion of low-dose ketamine prevents decreases in the body temperature of patients sedated with propofol. Ketamine has been shown to prevent shivering without producing hemodynamic alterations in patients undergoing regional anesthesia. [111] These data are consistent with the anti-shivering effects of premedication with tramadol observed in the present study as both ketamine and tramadol act as anti-shivering agents due to their action on NMDA receptors.[112]

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Regarding tramadol, many studies proved the efficacy of tramadol as antishivering agent including the following:

Mathews et al. compared administration of tramadol in doses of 2 and 1 mg/kg with normal saline for prevention of post-anesthetic shivering and found that the incidence of shivering was significantly lower in both tramadol groups compared to the control group.[113]

Shukla et al. compared the efficacy of administration of tramadol 0.5mg/kg and clonidine 0.5 μg/kg on post-spinal anesthesia shivering and found that both clonidine (0.5 μg/kg) and tramadol (0.5 mg/kg) effectively treated patients with post–spinal anesthesia shivering. [114]

Mohta et al. Concluded that tramadol 2 mg/kg had the best combination of antishivering and analgesic efficacy without excessive sedation and thus appeared to be a good choice to be administered at the time of wound closure to provide antishivering effect and analgesia without significant side effects in the postoperative period.[115]

Tsai et al. compared the efficacy of tramadol, amitriptyline, and pethidine for post-epidural anesthetic shivering in parturients, and concluded that both tramadol and pethidine showed a significantly faster response rate in the treatment of post-epidural anesthetic shivering when compared with amitriptyline in the dosage used; tramadol had a decreased incidence of somnolence when compared with pethidine. [116]

Aditi et al. compared the efficacy of tramadol versus pethidine to control post-regional anesthesia shivering and concluded that tramadol is effective in treating shivering under regional anesthesia due to its rapid onset, effective control, less recurrence rate and minimum side effects in a dose of 1 mg/kg when compared to Pethidine. [117]

Chan et al. found tramadol to be a promising drug in doses of 0.5 mg/kg and 0.25 mg/kg i.v., respectively, in controlling shivering under neuraxial blockade.[118] While, Gangopadhyay et al. found promising results with tramadol 1.0 mg/ kg i.v. in preventing shivering under spinal anesthesia.[119]

Ondansetron is a serotonin 5-HT3 receptor antagonist used mainly to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery.[120]

Kelsaka et al compared the efficacy of prophylactic ondansetron and pethidine in the prevention of shivering during and after spinal anesthesia. They reported that shivering was observed in 8% of the ondansetron group, 8% of the pethidine group, and 36% of the control group. [121]

5-HT_3 inhibition may have role to prevent shivering as a generalized thermoregulatory inhibition at the level of hypothalamus, where the bulk of thermoregulatory control occurs. Granisetron is 5-HT_3 receptor antagonist and this may explain its use for control of shivering. [122]

Our results coincide with Iqbal et al who compared the efficacy of granisetron versus pethidine for the prevention of postoperative shivering and concluded that granisetron 40mcg/kg was as effective as pethidine 25mg in preventing shivering related to general anesthesia. [123]

Also, Kim et al. performed a study to evaluate the effect of ramosetron, another 5-HT_3 antagonist, on shivering during spinal anesthesia in patients who had undergone knee arthroscopy. Shivering was observed in 7.7% in group R (ramosetron) and 34.6% in group S (saline) (P = 0.038). [124]

Sajedi and colleagues, carried out a study which evaluated the efficacy of granisetron in comparison with pethidine and tramadol in preventing post-anesthetic shivering in patients undergoing elective orthopedic surgery under general anesthesia and found that the number of patients with observable shivering was 57% in group P (placebo), 27% in group G (granisetron), 21% in group T (tramadol), and 18% in group M (Pethidine). Granisetron significantly reduced the incidence of shivering in comparison with placebo (P = 0.013). Although the frequency of shivering was higher with granisetron in comparison with tramadol and pethidine, it was not statistically significant (P > 0.05), so they concluded that the prophylactic use of granisetron 40 µg/kg is as effective as pethidine (0.4 mg/kg) and tramadol (0.1 mg/kg) in preventing post-anesthetic shivering without prolonging the emergence time from anesthesia. [125]

Our results did not coincide with Browning et al. who evaluated the prophylactic use of intravenous ondansetron 8 mg, which is another 5-HT_3 antagonist, before performing combined spinal-epidural anesthesia in women undergoing elective cesarean delivery and concluded that it does not decrease the incidence or severity of shivering.[126] This may be explained by the fact that the use of ondansetron in the previous study was prophylactic, however the drugs administered in the study are therapeutic for control of shivering not administered prophylactically.

Joyce et al. investigated the prophylactic use of ketamine in the prevention of anaesthetic-related shivering in 2 controlled trials enrolling a total of 250 patients. They concluded that ketamine was as effective as pethidine, but more effective than granisetron in reducing postoperative shivering. [127]

Our results coincide with those of Eldaba and Amr who studied the effect of pretreatment with intravenous granisetron 10 µg/kg intravenously diluted in 10 ml saline in reducing postoperative shivering after spinal anesthesia in children aged 2-5 years in comparison with placebo. They found that shivering did not occur in any patient in group G; it occurred in 15% of patients in group P.[128]

Also, our results did not coincide with those of Sayed et al. which found that prophylactic intravenous administration of 3 mg granisetron before spinal anesthesia in parturients undergoing elective cesarean section did not significantly decrease the incidence or severity of shivering. [129] However, this also can be explained that granisetron was used in this study as a prophylactic measure for shivering, while its use in our study is therapeutic.

Visible shivering intra-operatively in all groups was treated with intravenous pethidine in a dose of 25 mg.

In the current study, in group T, 0 % of the patients (i.e. 0 out of 30 patients) suffered shivering grades 2, 3 or 4 and none of the patients needed to be given pethidine intravenously.

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In group G, 13.33 % of the patients (i.e. 4 out of 30 patients) suffered shivering grades 2, 3 or 4 and needed to be given pethidine intravenously. There was no significant statistical difference between the two groups regarding the need to give pethidine to control visible shivering.

In our study, the incidence of side effects was significantly higher in the tramadol group than the granisetron group.

In the granisetron group, no side effects as bradycardia, hypotension or nausea and vomiting were noted. While in the tramadol group, 18 out of 30 patients had experienced nausea and vomiting and metoclopramide 10 mg intravenously was administered to these patients.

Tramadol cause nausea and vomiting mainly through stimulation of the Chemoreceptor Trigger Zone and increasing vestibular sensitivity.[130]

Our findings coincide with Gangopadhyay et al. who observed a significant number of cases (twenty out of thirty patients) of nausea and vomiting with tramadol. [119] Tramadol was used in their study to prophylactically prevent shivering after spinal anesthesia with dose of 1 mg/kg i.v which is the same dose used in the current study.

In the current study, the incidence of sedation was investigated in the two groups of study and it showed the same incidence of sedation in both groups (43.33%).

According to the differential depth of sedation in each of the two studied groups, it showed the following depth of sedation; firstly, in tramadol group, 20% of patients experienced sedation grade (2), 16.67% experienced sedation grade (3), 6.67% experienced sedation grade (4), 0% experienced sedation grade (5); secondly, in granisetron group, 30% of patients experienced sedation grade (2), 13.33% experienced grades (3), 0% experienced grades (4 or 5).

In summary, Both tramadol and granisetron are effective in the treatment of post-spinal shivering, while tramadol is more effective but at the cost of more side effects due to the higher incidence of nausea and vomiting.

SUMMARY

The current study was carried out in the Department of Orthopedics in El Hadara Main University Hospital, on 60 patients, aged 18-40 years old, ASA I-II, scheduled for elective orthopedic procedures with duration of 1 – 1.5 hours under spinal anesthesia, after the approval from the Local Ethical Committee and informed written consents from all the patients of the study.

Patients were randomly-allocated into two groups (30 patients each); group T (Tramadol group) and group G (Granisetron group).

All patients had carried out elective orthopedic procedures with duration of 1 – 1.5 hours under spinal anesthesia. Intravenous fluids preheated to 37°C were given to the patients before the spinal anesthesia. Subarachnoid anesthesia was instituted at either L3/4 or L4/5 interspaces. Hyperbaric bupivacaine (5 mg/ml) 15 mg was injected using 27G Quincke spinal needle. The study drugs were diluted to a volume of 10 ml and presented as coded syringes by an anesthesiologist who was blinded to group allocation just after intrathecal injection, all patients were given the study drug(s) as an i.v. bolus according to the group they were randomly assigned to.

Patients were randomly divided into two equal groups (30 patients each):

1. Patients in first group (group T) had received Tramadol 1 mg/kg.
2. Patients in second group (group G) had received Granisetron 40μ/kg.

The aim of this work was to compare the efficacy of tramadol versus granisetron for control of shivering during spinal anesthesia.

The results of the present study showed that:

Demographic Parameters

- **Age and Sex**

The age ranged between 19-39 and 19-38 year with a mean of 26.57±5.61 and 28.4±4.78 (years) for the two studied groups T and G respectively. Group T included 22 male and 8 females compared to 20 males and 10 females in group G.

There were no statistical significant differences between the two studied groups regarding age and sex.

- **Weight**

The weight ranged between 50-83 and 56-80 with a mean of 67.03±7.79 and 66.47±7.61 kilograms for group T and G respectively.

There was no statistical significant difference between the studied groups regarding weight.

Duration of surgery

The duration of surgery ranged between 60-90 and 60-90 (minutes) with a mean of 72.83±8.38 and 72.83±8.38 for group T and G respectively.

There was no statistical significant difference between the studied groups regarding the duration of surgery.

Hemodynamic Parameters

- **Heart rate**

On comparing the two studied groups, it was found that immediately before spinal anesthesia, heart rate ranged between 80-91 and 82-90 with a mean of 85.2±3.23 and 85.47 ± 2.84 (beats/minute) for group T and G respectively.

Statistically, it was found that there was no significant difference between the two studied groups at immediately before spinal anesthesia. However, all over the period of follow up, it was found that group T had lower value than group G which had higher value of heart rate.

- **Mean arterial blood pressure**

On comparing the two studied groups, it was found that the mean arterial blood pressure, immediately before spinal anesthesia, ranged from 82.0-97.0 (mmHg) in the two groups with a mean of 93.70±3.42 and 93.70±2.42 for group T and G respectively.

Statistically, there was no statistical significant difference between the two studied groups regarding MABP at all time periods of the operations.

- **Core Temperature Monitoring**

On comparing the two studied groups, it was found that immediately before spinal anesthesia, the core temperature ranged between 36.3-37.2 (ºC) with a mean of 36.85±0.23.

There was no statistical significant difference between the two studied groups regarding core temperature immediately before intrathecal injection, However, all over the period of follow up, it was found that group T had lower value than group G which had higher value of core temperature.

Onset of Shivering

Comparison between the two studied groups regarding onset of shivering showed that the onset of shivering in group T ranged between 3-15(minutes) with a mean of 7.53±3.01, while in Group G it ranged between 3-14(minutes) with a mean of 7.93±3.30. There was no statistical significant difference between the two groups.

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Shivering Score

Comparison between the two studied groups regarding shivering score showed that, there was no statistical significant difference between the two groups.

Comparison between the two groups as regards the need to give pethidine

Comparison between the two studied groups regarding the need to give pethidine showed that, there was no statistical significant difference between group T and G.

Time of Disappearance of Shivering

Comparison between the two studied groups regarding time of disappearance of shivering showed that, it ranged between 3-7 (minutes) in group T with a mean of 4.59±1.28, while in group G it ranged between 4-8 minutes with a mean of 5.67±1.24. There was significant statistical difference between the two groups.

Sedation Score

Comparison between the two studied groups regarding sedation score showed that, there was no statistical significant difference between group T and G**.**

Side Effects

Comparison between the two studied groups regarding the incidence of side effects showed that, there was no occurrence of braydcardia or hypotension in group T, however there was 18 patients out of 30 had experienced nausea and vomiting in the same group. In group G, no side effects happened either: bradycardia, hypotension or nausea and vomiting.

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CONCLUSION

From the present study, the following can be concluded:

1. The use of either tramadol or granisetron during spinal anesthesia was effective in the control of shivering.

2. Tramadol is more effective than granisetron in the control of shivering during spinal anesthesia, but with the disadvantage of more side effects in the form of nausea and vomiting.

3. Core body temperature is an important, but not the ultimate factor in controlling the incidence of postspinal shivering, as it may still occur in normothermic patients.

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