Prevention of shivering during regional anaesthesia: Comparison of Midazolam, Midazolam plus ketamine,Tramadol, and Tramadol plus Ketamine

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Abstract: Shivering is frequent during the post-anesthetic recovery period, and there is no clear consensus about the best strategy for its treatment. Post spinal shivering is very distressing for patients and may induce a variety of complications. In this prospective randomized, comparative, placebo controlled study, the efficacy of each of Midazolam, Midazolam plus ketamine,Tramadol, and Tramadol plus Ketamine for prophylaxis of post-spinal shivering was evaluated and compared to each other. One hundred AS A status I and II patients,who were undergoing elective orthopedic surgery under spinal anaesthesia,were included in the study. Patients randomly assigned to one of five groups; group C(n=20) received saline as a control, group M (n=20) received Midazolam 75 µg /kg, group MK(n=20) received Midzolam37.5µg/kg plus Ketamine 0.25 mg/kg ,group T(n=20) received Tramadol 0.5mg/kg and group TK(n=20) received Tramadol 0.25mg/kg plus Ketamine 0.25mg/kg . All of these drugs were diluted to volume of 5 ml and was given as an I.V. bolus immediately after intrathecal injection .The incidences of shivering in groups C,M,MK,T and TK were 55%,45%,5%,30% and 15% respectively(p-value was 0.003).The differences between group MK and groups C,M and T were statistically significant (p-value was <0.001,0.004 and 0.046 respectively) while difference between group MK and group TK was not significant (p-value was 0.302).Group TK also showed a statistically significant lower incidence of shivering when compared to group and M, but when compared with group T, the difference was not statistically significant. The incidence of shivering in group T was less than its incidence in groups C and M but this was not statistically significant. The difference between groups C and M was not statistically significant, so we concluded that I.V. midazolam plus Ketamine or Tramadol plus Ketamine is better than Midazolam or tramadol for prophylaxis of post spinal shivering. Midazolam plus Ketamine is superior to tramadol plus Ketamine.
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1. Introduction:

Post-anesthetic shivering is spontaneous, involuntary , rhythmic , oscillating, tremor-like muscle hyperactivity that increases metabolic heat production up to 600% after general or regional anesthesia (Ozaki et. al ;1994).

Post anesthetic shivering may cause discomfort to patients, and aggravate wound pain by stretching incisions and increase intracranial and intraocular pressure. Shivering may increase tissue oxygen demand by as much as 500% and accompanied by increase in minute ventilation and cardiac output to maintain aerobic metabolism.. This may be deleterious in patients with impaired cardiovascular reserve or a limited respiratory capacity. Shivering also may interfere with the monitoring of patients by causing artifacts of the ECG, blood pressure, and pulse oximetry (Honarmand A.and. Safavi M. R., 2008) .

Core temperature is maintained within a normal range during exposure to a cool environment because of sympathetically mediated vasoconstriction. Regional anesthesia produces vasodilatation, which facilitates core-to-peripheral redistribution of heat and the cool periphery is warmed at the expense of the core compartment. Thus, hypothermia from epidural anesthesia results from redistribution of heat from the core to the periphery (Hynson, .et al; 1991) .

Various opioid and non opioid agents were used to prevent and treat shivering, but they are not without side effects like hemodynamic instability, respiratory depression, nausea and vomiting. Variety of physical agents (radiant heat, space blanket) were also used to prevent post anesthetic shivering, but those cumbersome and with limited success (Glosten B. et al; 1993). Tramadol which is a centrally acting analgesic drug with µ-opioid agonist has been found effective in the prevention and treatment of shivering with less side effects than other µ-opioid agonists (Mohta et al., 2009). Midazolam is one of the benzodiazepines. It was found that it may decrease the incidence of shivering. Ketamine which is a competitive N-Methyl- D-Aspartate (NMDA)

receptors antagonist, has been found to be effective in preventing and treating post anesthetic shivering via central effects or via its effect on the hemodynamics of the cardiovascular system (Pitoni et al;2011)

2-Patients and methods

After obtaining institutional approval and written consent from all patients, this prospective, randomized, comparative and placebo controlled study was carried out in Tanta University hospital from Novamber2009 to July 2010 on one hundred ASA status I and II, patients between the ages of 21-60 years who were undergoing elective orthopedic surgery under spinal anesthesia.

Exclusion criteria:

Patients with thyroid diseases, cardiopulmonary diseases, neuromuscular diseases or psychological disorders were excluded from the study. Also, patients on narcotics , sedatives or any medication likely to alter thermoregulation. Patients with recent history of febrile illness and those with history of malignant hyperthermia.

Routine preoperative investigations including complete blood picture, renal function testes, liver function testes and coagulation profile.

Anesthetic technique: All patients did not receive any pre-medication. On arrival to the operating theatre, all patients had a venous cannula inserted. IV fluids in the form of lactated Ringer's solution were infused at a rate of 10 ml\Kg\h over 30 minutes before spinal anesthesia then the rate was reduced to 6 ml\Kg\ h. fluids were not warmed. The ambient temperature was maintained at 22-24 ^{0}C.

All patients had spinal anesthesia where 15 mg hyperbaric Bupivacaine 0.5% was instituted at either L3/L4 or L4/L5 using a 22 G quince spinal needle under complete aseptic conditions.

The patients were allocated randomly to one of five groups:

Group C (n=20): Received saline as a control.
Group M (n=20): Received midzolam 75 µg/Kg.
Group MK (n=20): Received midzolam 37.5 µg/Kg plus Ketamine 0.25 mg/Kg.
Group T (n=20): Received Tramadol 0.5mg/Kg.
Group TK (n=20): Received Tramadol 0.25mg/Kg plus ketamine 0.25 mg/Kg.

All of these drugs were diluted to volume of 5 ml and was given as an bolus immediately after intrthecal injection. Supplemental Oxygen was given via a face mask at a rate of 5 L /min during the operation. All patients were covered with one layer of surgical drapes over the chest thighs and calves during the operation and one cotton blanket over the entire body after the operation. After intrathecal injection the sensory and motor block were assessed with pinprick test every 5 minutes. When spinal anesthesia was established the presence of shivering was observed and graded by using a scale similar to that validated by Tsai and Chu where :

0= No shivering.
1=Piloerection or peripheral vasoconstriction but no visible shivering.
2= Muscular activity in only one muscle group.
3= Muscular activity in more than one muscle group but not generalized.
4= Shivering all over the body.

If shivering occurred, it was graded and recorded and if the grade was 3 or 4 after 15 min from the administration of the tested prophylactic drug, it was considered severe shivering and resce treatment in the form of IV 25 mg of pethidine was given.

Heart rate, respiratory rate, mean arterial blood pressure, peripheral oxygen saturation (SpO_2) and tympanic membrane temperature were recorded using standard non invasive monitors at 10 minutes intervals during the pre-and the postanesthesia period.

The degree of sedation was assessed according to a five-point scale where:
1=fully awake and oriented.
2=Drowsy.
3= Eye closed but responds to commands.
4=Eye closed but responds to mild physical stimulation.
5= Eye closed and not responding to mild physical stimulation.

Any other side effects was recorded and properly treated e.g. hypotension,nausea, vomiting and hallucination.

Statistical analysis:

Statistical presentation and analysis of the present study was conducted, using SPSS statistics (V.17.0;SPSS Inc., Chicago,IL, USA).

3-Results

This study was conducted after patients approval and consent on 100 patients presented for orthopedic surgery using spinal anesthesia. Part of the research was during anesthesia and surgery including clinical data such as the heart rate, mean arterial blood pressure, peripheral O_2 saturation, respiratory rate and core temperature.

The other part of the research was a trial to evaluate the prophylactic use of Midazolam ,Midazolam plus Ketamine ,Tramadol and Tramadol plus ketamine on the incidence of post spinal shivering ,where the patients were closely observed for detection of shivering and its grade. Also the

Patients were closely monitored for detection of any side effect.

Comparison of patients' demographic data showed that the differences among the five groups were not statistically significant as regard age, weight, BMI, sex, ASA status and duration of surgery (Table 1).

There was statistically insignificant differences among the five groups as regard the mean tympanic membrane temperature base value (*p*- value =0.067) while there were statistically significant differences among five groups at all the time intervals;10,20,30,40,50 and 60 of post –anesthesia period (*p*-value was <0.001,<0.001,<0.001,<0.001,0.001 and <0.001 respectively).

The change in the mean tympanic membrane temperature in group MK was statistically significant (*P*-value was <0.05) when compared with group C, group M and group T at all time intervals. However that change in temperature was not statistically significant (*P*-value was >0.05) when compared with group TK at any time.

The change in the mean tympanic membrane temperature in group TK was statistically significant (*P*-value was <0.05) when compared with group C and group M at all time intervals. However that change in temperature was statistically significant (*p*-value was <0.05) when compared with group T till 20 minutes of the post-anesthetic period, then at 30,40,50and60 minutes the change in temperature was statistically insignificant (*P*-value was 0.05).

The change in the mean tympanic membrane temperature in group T was not statistically significant when compared with group C and group M at any time of the post-anesthetic period (*P*-value was >0.05).

The change in the mean temperature in group M was not statistically significant (*P*-value >0.05) when compared with group C at any time. (Figure 1)

In our study MAP and heart rate values were not significantly different between the groups at any time of the post anesthesia period.

There was significant difference among the five groups as regard the incidence of shivering in the post –anesthesia period (*p*-value was 0.003).So, multiple 2×2 Fischers exact test were done to compare each to groups.

Group MK showed significant low incidence of shivering (5%) when compared with other groups, that incidence is less than that occurred in group TK (15%) but it was not statistically significant. Group TK also showed astatistically significant lower incidence of shivering when compared to group C and group M(*P*-value was 0.009and 0.041 respectively),but when compared with group T,less incidence of shivering was not statistically significant (*p*-value was 0.225). The incidence of shivering was less in the group T than group C and group M but was not statistically significant (*p*-value was 0.100 and 0.257 respectively). There was no statistically significant difference between the group C and group M(*P*=0.376) (Table2) .

The number of patients suffered from each grade of shivering was compared: No statistically significant differences were found among the groups as regard the grade of shivering (Fig 2).

No patients showed severe shivering in group MK that was statistically significant when compared with group C where 6 patients (30%) suffered from severe shivering (*P*-value was 0.010). When comparing groups; group MK with group M (10%),group T (5%) and group TK (5%),no statistically significant differences were found (*p*-value was 0.243,0.500 and 0.500 respectively). The incidence of severe shivering in group T was equal with that of group TK and low when compared with group C that was statistically significant (*p*- value was 0.045 for each group).The difference between group C and group M was not statistically significant in spite of the lower incidence in group M. Also the differences between group M and each of group T and group TK were not statistically significant (Fig 3) .

Statistical analysis showed that no significant differences among the groups as regard the incidence of hypotension, hallucinations ,nausea and vomiting(p-value was 0.0681,0.240,0.832 and 0.456 respectively) (Fig 4) .

Also in this study the number of patients suffered from each grade of sedation were compared, the median sedation score was significantly higher in group M (3) than group C (1) ,group MK (2),group T(1) and group TK (1.5) where *P*-value was <0.001,0.027,0.001 and 0.001 respectively. Group MK showed statistically significant higher median sedation score than group C and group T (*P*- value was<0.001 and 0.009 respectively) but not statistically different when compared with group TK (*p*- value was 0.167).

No statistically significant difference was found between group T and group TK though the higher median sedation score in group TK as *P*-value was 0.153.(table 3)

4-Discussion

Shivering is a frequent complication in the postoperative period. Shivering may occur as an adverse effect of surgery and anesthesia. It may be associated with an increase in oxygen consumption,

intraocular or intracranial pressure, and wound pain (Macintyre *et al., 1987and Sessler et al., 1994).* Thus, both the prevention of shivering and the treatment of established shivering should be regarded as clinically relevant medical interventions in the perioperative period. The mechanism which leads to shivering after regional anaesthesia is not very clear, but the probable mechanisms could be decrease in core body temperature secondary to sympathetic block; peripheral vasodilatation; increased cutaneous blood flow, which leads to increased heat loss through skin; cold temperature of operation theatre; rapid infusion of cold IV fluids; and effect of cold anaesthetic drugs upon the thermo sensitive receptors in the spinal cord (Chaturvedi S *et al.*,2002). The relative efficacy of pharmacological interventions to prevent this phenomenon is not well understood. Therefore, the present study was designed to detect the efficacy of each of midazolam, midazolam plus ketamine, tramadol and tramadol plus ketamine for prophylaxis of post spinal shivering .

In this study it was shown that I.V. midazolam (37.5 µg/Kg) plus ketamine (0.25mg/Kg) or tramadol (0.25mg/Kg) plus ketamine (0.25mg/Kg) is better than midazolam (75 µg/Kg) alone or tramadol (0.5 mg/Kg) alone for prophylaxis of post spinal shivering, whereas the midazolam plus ketamine combination is superior to tramadol plus ketamine combination as the former provides higher median sedation score. Kose et al.2008 and Gecaj-Gashi A.et al. 2010 found that Ketamine 0.5-0.75 mg/kg is more rapid than meperidine (25 mg) for the reduction of postoperative shivering, but the side effect profile may limit its usefulness. Ketamine produces undesirable psychological reactions termed emergence reactions. The common manifestations are vivid dreaming, extracorporeal experiences (sense of floating out of body), hallucinations and illusions. However in the current stuy the incidence of hallucinations in patients receiving ketamine was very low (10%in group TK and 5% in group MK) that was not significant when compared to the control group. This can be explained by the use of low dose of ketamine in the present study (0.25 mg/kg). This supported by pervious studies by Honarmand *et al.,* 2008 and Sagir *et al.,* 2007 where similar dose of ketamine was used with no incidence of hallucinations.

Tramadol activates the mononergic receptors of the descending neuraxial inhibiting pain pathway. The anti-shivering action of tramadol is probably mediated via its opioid or serotonergic and noradrenergic activity or both (Mathews et al.,2002 and Bilotta et al.,2002).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(Mohta M *et al.*,2009). Tramadol is an opioid analgesic with opioid action preferably mediated via µ (mu) receptor with minimal effect on kappa and delta binding sites.

Kurz, *et al.,* 1995 studied the effect of midazolam on thermoregulation and found that reduction in heat production after administration of midazolam is less than that after induction of anesthesia with clinical doses of volatile anesthetics , propofol, and opioids .Also, they reported that midzolam, even in plasma concentrations far exceeding those used routinely, produces minimal impairment of thermoregulatory control. This explains the lower incidence of shivering observed in our patients receiving midazolam. However, in another study by Grover *et al.,* 2002 they showed that administration of midazolam towards the end of the anesthetic procedure doesn't prevent shivering but it subsides earlier in the postoperative period. In the present study, post-spinal shivering occurred in 55% of patients of group C. In group M shivering occurred in 45% of patients which was lower when compared with group C. Also the incidence of severe shivering (score≥3) was not significantly different in both groups. This incidence was consistent with the failure of midazolam to prevent or minimize the core hypothermia. The incidence of shivering in group T was 30% of patients which was significantly lower than that of the control group C. Adding small dose ketamine to midazolam or tramadol enhanced their anti-shivering effect, the incidence is lowered to 5% in group MK and 15% in group TK. The median sedation score was significantly higher in group M than group C, group MK, group T and group TK.
Group MK showed statistically significant higher median sedation score than group C and group T but not statistically significant difference was found between group T and group TK. In this connection, the patients of group M and group MK have more preoperative comfort than other groups.

It is clear from the present study that adding Ketamine to midazolam or Tramadol; enhanced their anti-shivering effect. This suggests that Ketamine has a synergistic anti-shivering effect when combined with any of the two drugs. So, further studies are needed to find out the exact mechanism of interaction.

In conclusion: I.V. midazolam plus ketamine or tramadol plus ketamine is better than midazolam or tramadol for prophylaxis of post – spinal shivering, whereas the midazolam plus ketamine combination is superior to tramadol plus ketamine combination.

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Table 1: patients' demographic data, ASA status and duration of surgery.

	GROUP C	GROUP M	GROUPMK	GROUPT	GROUPTK	P-VALUE ANOVA
Age (years)	44.04±14.90	42.944±14.07	35.36±13.99	41.86±14.23	46.17±9.07	0.126
Weight (Kg)	76.53±13.72	75.66±11.36	4.75±10.66	73.94±13.13	76.94±12.86	0.951
BMI(Kg\m2)	29.64±4.28	28.61±**7.46**	28.89±5.73	27.67±6.70	30.28±5.84	0.710
Duration of surgery/min	94.09±12.58	95.12±10.47	86.39±10.57	87.95±11.15	89.72±14.31	0.096
Sex (m\f)	10/10	12/8	13/7	11/9	12/8	Chi-squared x^2 0.899
ASA(I/II)	19/1	20/0	20/0	18/2	20/0	0.240

BMI = Body mass index

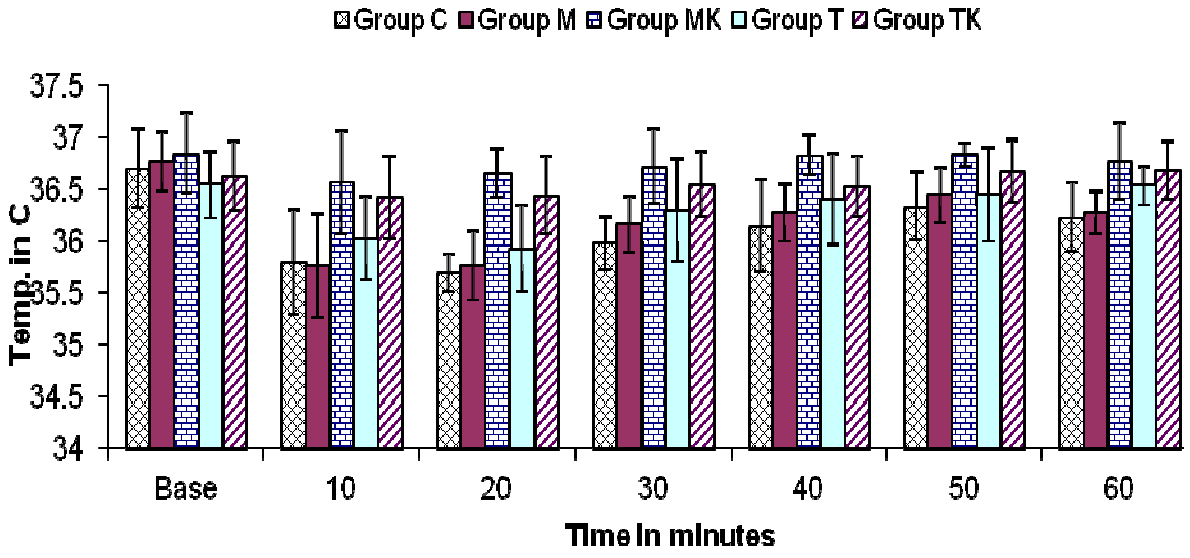

Figure1: Changes of tympanic membrane temperature in the five groups

Table2: overall incidence shivering in the five groups.

	GROUP C	GROUP M	GROUP MK	GROUP T	GROUP TK	Chi-square	
Shiverers	11 (55%)	9(45%)	1(5%)*	6(30%)	3(15%) ¥	x^2	P
Non-Shiverers	9 (54%)	11(55%)	19(95%)	14(70%)	17(85%)	16.190	0.003

Value are expressed as number of patients and percent (%)

*Significant in comparison with group C, group M and group T (P-value <0.05).

¥ Significant in comparison with group C, group M (P-value <0.05).

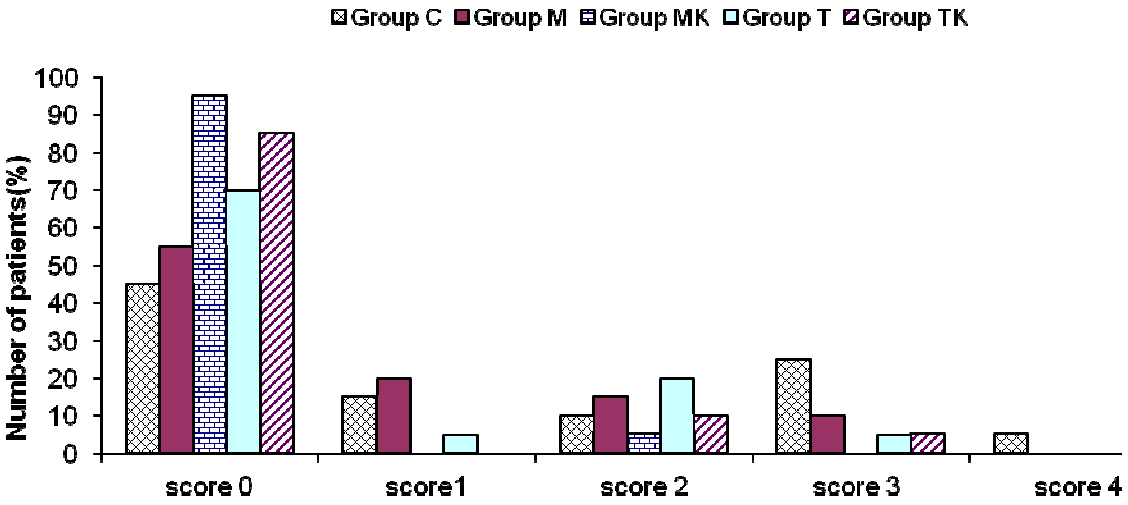

Figure2: Shivering score of all patients in all five groups

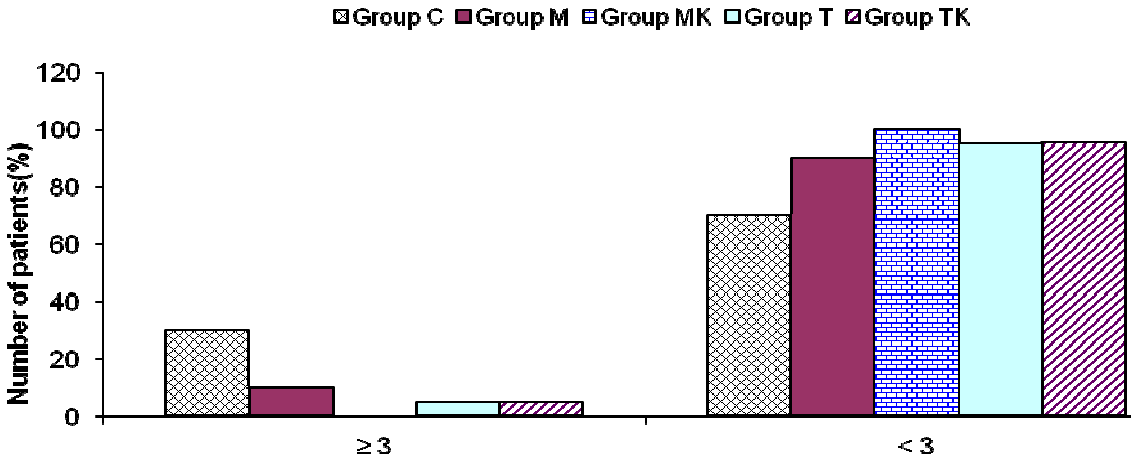

Fig 3: Incidence of severe shivering (score≥3) in the five groups. Values are expressed as number of patients (%)

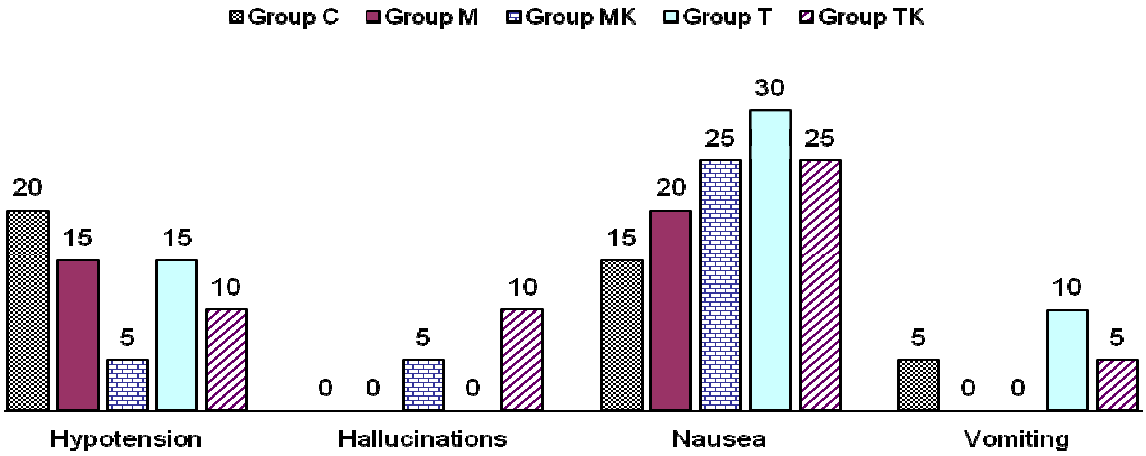

Figure 4: Incidence of complications in the five groups, values are expressed as number of patients (%)

Table 3: Sedation score of all patients in the five groups

Sedation score	GROUP C N=20	GROUP M N=20	GROUP MK N=20	GROUP T N=20	GROUP TK N=20	Chi-square	
						□²	P
1	20 (100%)	3 (15%)	7(35%)	14(70%)	10(50%)	34.380	<0.001
2	0	4(20%)	7(35%)	6(30%)	8(40%)	10.667	0.031
3	0	9(45%)	5(25%)	0	2(10%)	21.875	<0.001
4	0	4(20%)	1(5%)	0	0	12.632	0.013
5	0	0	0	0	0	Not tested	
Median (range)	1(1-1)	3(2-3)*	2(1-3) ¥	1(1-2)	1.5(1-2)		

Value are expressed as number of patients and percent (%)
*statistically significant when compared with other groups (P-value <0.05).
¥ Statistically significant when compared with group C and group T (P-value <0.05).