THE EFFICACY OF A SINGLE DOSE OF PETHIDINE, FENTANYL AND MORPHINE IN TREATING POSTANESTHESIA SHIVERING

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ABSTRACT

Postanesthesia shivering is an undesirable event that may induce a variety of adverse consequences including patient discomfort, increased oxygen consumption and wound pain. Thus, its pharmacological treatment should be regarded. The purpose of this study was to compare the efficacy of morphine, fentanyl and pethidine for the treatment of postanesthesia shivering. Fifty patients who developed shivering were treated in a randomized double blinded manner with an intravenous bolus dose of 2 or 4 mg morphine, 25 or 50 mg pethidine, and 50 μg fentanyl. Then, they were monitored for 30 minutes and the shivering suppression grade, the time taken to stop shivering, the shivering cessation time, recurrence of shivering and opioid side effects were evaluated. Core body temperature was measured immediately before, and at 15 and 30 minute after administering the drug. The groups did not differ significantly regarding shivering suppression grade, shivering cessation time, and recurrence of shivering. There was a significant difference in the time taken to stop shivering between groups. Following injection of the drugs, the core temperatures increased in the five groups with statistical difference. All opioids were effective in treating postanesthesia shivering in a similar extent.

Keywords: Postanesthesia shivering, opioids, morphine, pethidine, fentanyl, hypothermia.

INTRODUCTION

Postanesthetic shivering (PAS) is an involuntary muscular activity that is observed in 5-60 % of patients recovered from general anesthesia and, along with nausea and vomiting, is the main causes of patients discomfort following anesthesia. Some even find it worse than surgical pain and remember the shaking experience for years following surgery (Crossley, 1992; Wallis, 2000; Vogelsang, 1994). The other disadvantageous effects of PAS included increased oxygen consumption and carbon dioxide production with resultant increase in cardiac output and minute ventilation, increase in intraocular and intracranial pressures, exacerbation of postoperative wound pain, and difficulty in effective use of monitoring equipments (Buggy and Crossley, 2000). A number of pharmacological interventions have been studied for the treatment of shivering including pethidine, clonidine, doxapram, ketamine, tramadol, nefopam, physostigmine, and other opioids (Ihn *et al.,* 2008; Kranke *et al.,* 2002). Among them, pethidine has been more extensively evaluated and is the drug of choice to treat shivering in the post anesthetic period (Kranke *et al.,* 2003; De Witte and Sessler, 2002). The aim of the present study was to compare the efficacy of morphine and fentanyl with pethidine for the treatment of PAS.

MATERIALS AND METHODS

This prospective, randomized, double–blind, controlled trial was approved by the Local Hospital Ethics Committee and the patient's written informed consent was obtained on the possibility of pharmacologic management of postoperative shivering. Patients had undergone elective general, thoracic, or ENT surgery and were anesthetized using balanced or total intravenous

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anesthesia (TIVA) techniques. All patients received fentanyl 1 µg/kg before induction of anesthesia as their only opioid. After operation the patients' trachea was extubated and they were transported to the recovery room. During recovery, patients were covered by a single sheet and were not actively warmed. The temperature of the operation and recovery rooms was maintained at 22-23°C throughout the study period. In the recovery room an experienced investigator assessed all patients for occurrence of shivering according to a four point visual assessment scale (Baumann and Sung, 1992):

0: none
1: mild, minimal fasciculation on face and neck
2: moderate,visible tremor involving head, neck, shoulders and/or extremities
3: severe, generalized and visible shaking

Thereafter, fifty American Society of Anesthesiologists (ASA) physical status I or II patients who developed visible shivering (grade = > 2) that lasted for 2 to 3 minutes were assigned to one of the five treatment groups (n= 10 each) by random drawing of a sealed envelope which was generated by a table of random numbers to receive an intravenous bolus dose of 2 or 4 mg morphine, 25 or 50 mg pethidine, and 50 µg fentanyl. Then the identical syringes containing the study drugs were prepared and injected by recovery room staffs that were unaware of the treatment received by the patient.

The criteria for inclusion were: age 14 to 65 years old, extubated and breathing spontaneously, responsive to verbal stimulation, and not received an opioid for postoperative pain. The exclusion criteria were: fever, positive history of drug abuse, prolonged use of opioids, neurological and psychiatric disorders, physical status III or IV, hemodynamic instability, and positive history of cardio respiratory disease.

After administration of study opioids, the patients were observed for treatment effects every subsequent 1 minute for 30 minutes by an anesthetist who was blinded to the drug administered. PAS response to treatment was measured by a graded visual suppression scale (Vogelsang and Hayes, 1992):

0= shaking continues
1= shaking is diminished
2= shaking was disappeared

The time taken to stop shivering after drug administration, the duration of cessation of shivering, recurrence of shivering, body temperature, and opioid-related side effects were also evaluated. Body temperature was measured in the axilla with a mercury thermometer in three phases; immediately prior to administering the treatment (T0), at 15 (T15), and at 30 minute (T30) after the drug was injected. At the end of 15 minutes after injection of the medication, patients who still had a shivering grade = >2 were removed from the study and covered with a warming blanket, and if ineffective, additional dose of pethidine 25 mg IV was given. The study considered complete after 30 minutes of the treatment.

Side effects including respiratory depression, nausea, vomiting, sedation, and pruritus were noted. Sedation was graded as: 1-fully awake, 2-drowsy, 3-eyes closed but arousable to command, 4- eyes closed but rousable to mild physical stimulation, 5- eyes closed and unrousable to mild physical stimulation. Other recorded data consisted of type and duration of surgery, patients' age, weight, height and gender. The same blinded observer recorded all data.

Results are expressed as mean ± SD and number. P-value less than or equal to 0.05 were considered statistically significant.

RESULTS

Fifty patients (31 men and 19 women) were studied. Mean ± SD age of all patients was 32.62 ± 12.62 years (range of 14 to 61 years), weight 67.3± 11 kg, height 168.22± 8.4, and the duration of surgery was 193± 91.62 minutes. The demographics, clinical characteristics, surgery and anesthesia data were similar between the five

Table 1: Patient characteristics and preoperative data in the five groups (data are expressed as number and mean ±SD.

	Pethidine 25mg	Pethidine 50 mg	Morphine 2 mg	Morohine 4 mg	Fentanyl 50µg	P value
Age(yrs)	39 ± 15.7	35.5 ± 10	28 ± 10	27.2 ± 9.24	33.7±15	*0.171*
Weight (kg)	66.7± 10	69±11.4	66.7± 6	73.25 ± 8	61±15.43	*0.154*
Gender F:M	5/5	4/6	3/7	4/6	3/7	*0.65*
Height (cm)	167± 8.4	168 ± 8	173.2 ± 5	169 ± 6.65	164.4±11.62	*0.197*
ASA class ½	6/4	2/8	2/8	3/7	2/8	*0.17*
Duration of surgery (min)	204± 88	207±119.5	204± 61	136.5± 61	213.5±108	*0.312*
Anesthesia methodTIVA/Balance	5/5	2/8	2/8	8/2	4/6	*0.072*
Transfusion Yes/No	3/7	2/8	0/10	0/10	0/10	0.064

There are no significant differences between five study groups (P > 0.05).

groups (table 1). Prior to administration of study medication, groups were also similar in terms of shivering grade (P=0.48), type of surgical procedures (P=0.266), sedation score (P=0.759), and body temperature (T0) (table 2). Treatment failure requiring additional dose of pethidine 25 mg IV occurred in 3 patients of the morphine 2 mg, 1 of the pethidine 25 mg and 1 of the fentanyl 50 µg group with no significant difference.

At 15 and 30 minutes after treatment, there were also no significant differences between groups with regard to the shivering suppression grade, shivering cessation time, recurrence of shivering and degree of sedation (table 3). 2 patients in the pethidine 25 mg, 3 in the fentanyl 50 µg, and 1 in the morphine 2 mg group had a recurrence of shivering although the difference was not statistically significant between groups.

There was a significant difference in the time taken to stop shivering between groups (table 3). The 50 mg dose of pethidine significantly produced a more rapid anti-shivering effect while morphine 2 mg produced a slower effect. The 8/10 post-treatment patients who received pethidine 50 mg stopped shivering within less than 2 minute (P=0.017).

At both 15 and 30 minutes after injection of the opioids, the body temperatures increased in the five groups with statistical difference (T30>T15>T0) (fig. 1, table 2). In addition, in the pethidine 25 mg and 50 mg groups respectively, increase in body temperature was significantly lower than the other groups. Patients in the morphine 4 mg group had significantly higher temperatures.

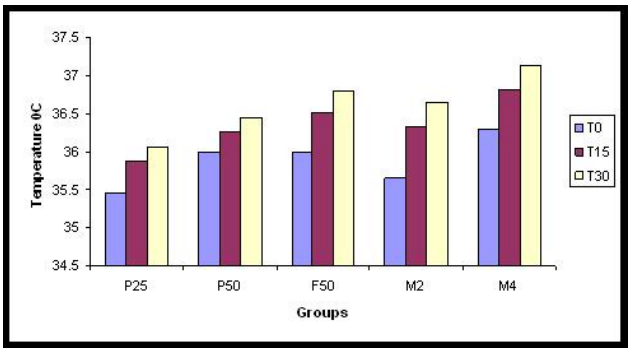

Fig. 1: Before treatment, body temperature (T0) was similar among groups (P>0.05). Mean T values at 15 (T15) and at 30 min (T30) after treatment, increased with significant differences among five groups (P<0.05). P25: Pethidine 25mg, P50:pethidine 50 mg, F2: fentanyl 50 µg, M2:morphine 2mg, M4:morphine 4mg groups.

Table 2: Mean ±SD body temperatures (^{o}C) in five groups.

Time	Pethidine 25	Pethidine 50	Morphine 2	Morphine 4	Fentanyl 50	P value
T0	35.45± 0.43	35.94± 0.40	35.65± 0.33	36.30± 0.27	36 ± 0.62	0.08
T15	35.9± 0.64	36.26±0.44	36.34± 0.35	36.81± 0.36	36.52± 0.52	0.002*
T30	36.07± 0.65	36.45± 0.40	36.65± 0.51	37.14± 0.55	36.8± 0.32	0.001*

*P< 0.05: significant. T0: Temperature before treatment. T15: Temperature at 15 min after treatment, T30: Temperature at 30 min after treatment

Table 3: Outcomes following administration of the study opioids (n=10 in each group). Data are mean ± SD or number of patients.

	Pethidine 25 mg	Pethidine 50 mg	Morphine 2 mg	Morphine 4 mg	Fentanyl 50 µg	P value
shivering cessation time (min)	25.5 ± 6.7	28.45 ± 1.6	22 ± 7	25.6 ± 1.8	20 ± 10.63	0.063
Time to shivering suppression (min)	2.66 ± 2	1.54± 1.6	5.71 ± 4.46	4 ± 1.56	2.22 ±1.47	0.007*
Recurrence of shivering						
Yes	2	0	1	0	3	0.087
No	7	10	6	10	6	
Shivering suppression grade at 15 min						
0	1	0	3	0	1	0.237
1	1	0	1	2	1	
2	8	10	6	8	8	
Shivering suppression grade at 30 min						
0	1	0	4	0	2	0.105
1	2	0	1	0	1	
2	7	10	5	10	7	

There was a significant difference between groups in terms of time taken to suppress postanesthesia shivering (P = 0.007). The 50 mg dose of pethidine significantly had a more rapid onset than the other groups for treating shivering.

At 15 minutes after administering the medications, mild nausea significantly developed in more patients treated with pethidine 50 mg (4 of 10 patients) (P= 0.006) and in one patient treated with pethidine 25 mg, not needing a specific treatment. At 30 minutes, one patient in the morphine 2 mg vomited and one patient in the pethidine 25 mg group had transient nausea. No other opioid related side effects (respiratory depression, pruritus, and sedation) were seen. Almost all patients in the five groups had a sedation score of ≤ 3 during the study period (P>0.05).

DISCUSSION

PAS remains an undesirable consequence of anesthesia. It develops during early emergence from general anesthesia as patients are transported from operating room, or shortly after arrival in the recovery room and may continue for minutes to hours when not treated. In addition to causing the remarkable discomfort and aggravation of surgical pain, the main physiological consequences of the PAS include an increase in cardiac workload and minute ventilation. Patients having limited myocardial oxygen supply may not be able to increase these cardio respiratory parameters adequately (Alfonsi, 2001).

Many drugs have been studied for the management of PAS where pethidine 25 mg has been the most effective drug widely used to treat PAS (Buggy and Crossley, 2000). In this study, we found that all opioids effectively managing PAS to a similar extent. We included group pethidine 25 mg as a control group in our study because we considered it unethical to leave shivering patients untreated.

The exact etiology of PAS still remains unclear. It is believed that the most common cause of PAS is a thermoregulatory response to intraoperative hypothermia (T<=36.5^{o}C). However, it may also occur in normothermic patients (Buggy and Crossley, 2000; Kranke *et al.,* 2003). During general anesthesia, the thermoregulatory threshold for shivering response to core hypothermia is lowered by anesthetic drugs. Subsequently, during initial phase of recovery from anesthesia, when shivering threshold returns towards normal, shivering is triggered and becomes visible (De Witte and Sessler, 2002; Alfonsi, 2001). Likewise, our shivered patients were hypothermic on arrival in the recovery room (T0 was near 36^{o}C) and shivering was preceded by hypothermia.

Opioids treat shivering via the μ or κ opioid receptors and exert their antishivering effects via decreasing the shivering threshold (Kurz *et al.,* 1995; Alfonsi *et al.,* 1998; Alfonsi *et al.,* 2009). κ opioid receptors may play a more important role than μ receptors in treating shivering. Pethidine is mainly a κ agonist and inhibits shivering better than the equianalgesic doses of pure μ receptor agonists, such as morphine, fentanyl, alfentanil, and sufentanil. The special antishivering effect of the pethidine is related to its activity at κ receptors (Vogelsang and Hayes, 1992; Kurz *et al.,* 1995; Kurz *et al.,* 1997; Alfonsi *et al.,* 1995; Kurz *et al.,* 1993; Wrench *et al.,* 1997a). In our study, cessation of shivering was not associated with re-establishment of normothermia in the groups pethidine 25 mg and 50 mg (T= 36 ± 0.64 and 36.26 ± 0.44, respectively). Furthermore, after treatment, an increase in the mean temperature was lower in both pethidine groups than in the other groups. Our results indirectly support those observations that indicated PAS inhibition with pethidine may be more related to reduction in shivering threshold than reestablishment of normothernia (Kimberger *et al.,* 2007).

Our findings agree with those of previous studies on the efficacy of pethidine 25-50 mg for the treatment of shivering (Baumann and Sung, 1992; Vogelsang and Hayes, 1992; Schwarzkopf *et al.,* 2001; Tsai and Chu, 2001). Though, we found that the antishivering effect of morphine and fentanyl was similar to that of pethidine. Similarly, Baumann and Sung (1992) found no difference between pethidine and fentanyl in management of PAS. Likewise, in another study by Alfonsi *et al* (1995), pethidine and to a lesser extent fentanyl effectively treated PAS without reinstitution of normothermia. In contrast, Pauca *et al* (1984) reported that pethidine 25 mg was significantly superior to equivalent doses of morphine and fentanyl in the treatment of PAS, and the termination of shivering was associated with the increase in core temperature. Furthermore, Vogelsang and Hayes showed that morphine 2 to 4 mg could not suppress PAS (1992).

In the present study, shivering was stopped within one minute in patients given 50 mg dose of pethidine without recurrence, although the differences did not reach statistical significance between the groups. This finding is in accordance with studies indicated that larger doses of pethidine can provide a rapid and potent antishivering effect (Wrench *et al.,* 1997 b; Wang *et al.,* 1999).

According to our results, the duration of cessation of shivering was significantly shorter and shivering restarted in more patients in the fentanyl group compared to others. The reason may be due to higher lipid solubility of fentanyl that causes a rapid movement from the site of action to the systemic circulation that could shorten the duration of action of fentanyl (Alfonsi *et al.,* 1995).

In our study, we observed that the incidence of nausea after administration of 50 mg of pethidine was significantly higher than the dose of 25 mg. Since postoperative nausea can be more disturbing than shivering, it seems that PAS can be safely and adequately treated by 25 mg dose of pethidine.

One criticism of this study is that the chosen doses of morphine and fentanyl were slightly under equianalgesic doses of pethidine. However, as the dose difference was small, we think that it did not influence the results of this trial. Another criticism was that the administered doses of study opioids were not based on patient weight, although the small standard doses being given to our patients was chosen based on previous studies (Vogelsang and Hayes, 1992; Wrench *et al.,* 1997 b).

In conclusion, all studies opioids were found to be effective in treating PAS in a similar extent. Our results confirm that inhibition of postanesthesia shivering with opioids was not connected with re-establishment of normothermia.

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