Available online at www.journalijmrr.com

INTERNATIONAL JOURNAL OF MODERN RESEARCH AND REVIEWS

Int. J. Modn. Res. Revs.

Volume 2, Issue 10, pp 379-384, October, 2014

ISSN: 2347-8314

A COMPARATIVE STUDY OF CLONIDINE AND TRAMADOL FOR THE CONTROL OF POST SPINAL ANAESTHESIA SHIVERING

***[1]V.Aravind, [2]M.Dhakshinamoorthy and [3]C.Dhanasekaran**

*[1]Post Graduate, Department of Anaesthesiology, Rajah Muthiah Medical College & Hospital, Annamalai University, Annamalainagar 608 002, Tamilnadu, India

[2]Professor, Department of Anaesthesiology, Rajah Muthiah Medical College & Hospital, Annamalai University, Annamalainagar 608 002, Tamilnadu, India

[3]Professor Department of Anaesthesiology, Rajah Muthiah Medical College & Hospital, Annamalai University, Annamalainagar 608 002, Tamilnadu, India

Article History: *Received 5th September,2014, Accepted 6th October, 2014, Published 7th October,2014*

ABSTRACT

INTRODUCTION: Spinal anaesthesia is widely used as a safe anaesthetic technique for both elective and emergency operations. Shivering is one of the most common complications, reported in 19%-33% of patients undergoing surgery under spinal anaesthesia. Shivering is very unpleasant, physiologically stressful for the patient undergoing surgery, and some patients find the accompanying cold sensation to be worse than the surgical pain. Control of post spinal shivering is essential for optimal perioperative care. **AIMS AND OBJECTIVES:** To compare the efficacy and safety of intravenous clonidine (1µg/kg) and tramadol (1mg/kg) for control of shivering under spinal anaesthesia. **MATERIALS AND METHODS:** After obtaining ethical committee clearance and written informed consent, 80 patients from either gender, aged between 15-40 yrs, ASA grade I or II undergoing various surgeries under subarachnoid block who subsequently developed shivering were included. Group T (n=40) received 1mg/kg Tramadol intravenously. Group C (n=40) received 1µg/kg Clonidine intravenously. The efficacy and response rate of the study drugs were evaluated and recorded. Grade of shivering, disappearance of shivering, haemodynamics and side effects like, nausea, vomiting, hypotension, bradycardia, dry mouth, sedation, skin rash and headache, if present, were recorded at scheduled intervals. All data were analyzed by using the Chi square test, Independent "t" test and Fischer exact test. **RESULT: S**hivering control occurred in both groups but Tramadol group had early control (4.58±0.59 mins) and late recurrence, Clonidine group had delayed control (8.02±5.15 mins) and early recurrence (P=0.018). Haemodynamic parameters were maintained within 15% of baseline values in both groups. Complications like nausea, vomitimg occurred in both groups but no significant difference. Tramadol was found to have less sedation than clonidine (sedation level-3, group C-10%). **CONCLUSION:** We conclude that 1mg/kg of iv tramadol is an ideal alternative to 1µg/kg iv clonidine to control postspinal shivering by providing early control and delayed recurrence of shivering with minimal side effects.

Keywords: Clonidine, Postspinal shivering, Tramadol

1.INTRODUCTION

Spinal anaesthesia is widely used as a safe anaesthetic technique for both elective and emergency operations. Shivering is one of the most common complications of a central neuraxial blockade, due to impairment of thermoregulatory control [1], reported in 19%-33% of patients undergoing surgery under spinal anaesthesia [2,3] Shivering is a potentially serious complication, resulting in increased metabolic rate; increased oxygen consumption (up to 600%) along with raised carbon dioxide (CO_2) production; ventilation and cardiac output; adverse postoperative outcomes, such as wound infection; increased surgical bleeding; and morbid cardiac events. It causes arterial hypoxemia, lactic acidosis, increased intraocular pressure (IOP), increased intracranial pressure (ICP); and interferes with pulse rate, blood pressure (BP) and electrocardiographic(ECG) monitoring.[4,5,6] Perioperative hypothermia is the primary cause, which occurs due to neuraxial anaesthesia-induced inhibition of thermoregulatory mechanism. Shivering occurs as a thermoregulatory response to hypothermia or muscle activity with tonic or clonic patterns, and various

**Corresponding author V.Aravind, Post Graduate, Department of Anaesthesiology, Rajah Muthiah Medical College, & Hospital, Annamalai University, Annamalainagar – 608 002, Tamilnadu, India*

frequencies have been noticed.[6] Control of post spinal shivering is essential for optimal perioperative care, which can be achieved either by oral or parental medications. Non pharmacological method which use specialised equipments to prevent or to control shivering are expensive and are not practical in all clinical settings.[7] Unfortunately, no gold standard treatment is known for shivering as the administration of all the available drugs is associated with various adverse effects. During the last decade, Tramadol has become a favoured and commonly used drug for post-spinal anaesthesia shivering. However, it has many adverse effects like nausea, vomiting, dizziness etc., which cause further discomfort to the patient.[8,9] Clonidine is another agent which has gained popularity during the last few years. Various studies, which have been conducted to compare them have concluded that clonidine has better efficacy and less adverse effects as compared to tramadol.[8,9]

2.METHODOLOGY

In the present randomized controlled prospective study a total of 80 patients from either gender, aged between 15-40 yrs, of ASA grade I or II undergoing various surgeries under subarachnoid block who subsequently developed shivering were included. The patients were randomly divided into 2 groups Group T - 40 patients who received 1 mg/kg Tramadol intravenously. Group C - 40 patients who received 1 µg/kg Clonidine intravenously. **Inclusion Criteria**: a) Patients from either gender aged between 15-40 years. b) ASA grade I - II undergoing various surgeries under subarachnoid block who developed shivering after anaesthesia. c) Shivering of grade 2-4 (Crossley and Mahajan scale) lasting for a minimum period of 2 minutes. d) Patients who have a valid informed written consent. **Exclusion Criteria:** a) Patients who did not give a valid informed consent; b) Patients not belonging to the above mentioned age or ASA grade; c) Patients with fever, significant cardiovascular, renal, hepatic, respiratory, thyroid, neurological disorders, autonomic neuropathies, a need for blood transfusion during surgery; d) Patients with an initial body temperature > 38°C or < 36°C; e) Patients with known hypersensitivity to tramadol or clonidine; f) Patients with known history of alcohol and substance abuse; g) Patients who develop shivering even before administering spinal anaesthesia; h) Patients requiring supplementation with general anaesthesia. **Anaesthetic management:** The ambient temperature was measured by a wall mounted thermometer. The ambient temperature was maintained at 24°C – 26°C. Baseline vital parameters were recorded. IV access was obtained with 18 G cannula and IV fluids started. The volume of the local anaesthetic, volume of preloading fluid, use of vasopressors were determined by the attending anaesthesiologist, and was not affected by inclusion in the study. Volume of preloading intravenous fuids, use of mephenteramine for hypotension and the dose of local anaesthetic were determined by the attending anaesthesiologist and were not affected by enrollment in the study. All preloading fuids and drugs were stored and administered at room temperature. Oxygen at rate of 4 Litre/min was administered through face mask to all the patients. Subarachnoid block was instituted either in L2-L3 or L3-L4 interspace. 0.5% hyperbaric Bupivacaine Hydrochloride was used in all cases for subarachnoid block. . The treatment drugs were diluted to a volume of 5 ml in a 5 ml syringe and presented as coded syringes by an anaesthesiologist who was blinded to the group allocation. Side effects like nausea, vomiting, bradycardia (<50/min), hypotension (>20% of baseline), dizziness and sedation score were recorded. Skin rash and headache, if present, were recorded. If patients developed nausea and vomiting, iv metoclopramide 10 mg was administered. Monitoring of NIBP, pulse oximetry, ECG, was done throughout the procedure. A total of 80 cases fitting the above criteria were studied. They were randomly divided into one of the two groups. Group T - 40 patients receiving 1 mg/kg Tramadol iv. Group C - 40 patients receiving 1 µg/kg Clonidine iv. Parameters compared: Shivering was graded as follows. Crossely and Mahajan scale was used to assess the degree of shivering.[12] Grade 0 - No shivering; Grade 1 - No visible muscle activity but piloerection, peripheral vasoconstriction, or both are present(other causes excluded); Grade 2 - Muscular activity involving only one muscle group; Grade 3 - Muscular activity involving two or more than two muscle groups but not involving whole body; Grade 4 - Shivering involving entire body, bed shaking. The drug was administered by another anaesthetic personnel who is blinded to whether the drug contains clonidine or tramadol. The same person assessed the effect of the drug administration based on the format provided. All the patients were assessed for shivering grades, its disappearance, haemodynamic status, and complications if any. Recurrence of shivering was also noted. The attending anaesthetist recorded the time in minutes at which shivering started after spinal anaesthesia (onset of shivering), severity of the shivering, time to disappearance of shivering (in minutes) and response rate (shivering ceased after treatment in 15 minutes). Patients who did not respond or in whom recurrence of shivering occurred were treated with additional dose of clonidine (1 µg/kg IV) or tramadol (1 mg/kg IV) in the respective groups, if required. Side effects like nausea, vomiting, bradycardia (<50/min), hypotension (>20% of baseline), and sedation score were recorded. Sedation characteristics were noted and graded according to the Ramsay's sedation scores as follows: 1.Awake and anxious, agitated, or restless; 2.Awake, cooperative, accepting ventilation, oriented, tranquil; 3.Awake; responds only to commands; 4.Asleep; brisk response to light glabellar tap or loud noise; 5.Asleep; sluggish response to light glabellar tap or loud noise stimulus; 6.Asleep; no response to light glabellar tap or loud noise. Statistical Methods: Continuous measurements are presented on Mean ± SD and categorical measurements are presented in Number (%). Student's T Test has been used to find the significance of study parameters between two groups of patients, Chi-square/ 2x3 Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The value of $P < 0.05$ was considered as statistically significant.

3.RESULTS:

A total of 80 patients, aged between 15-40 yrs, of ASA grade I or II were enrolled in the present study and were randomized into two groups of 40 each(n=40). Group T - 40 patients who received 1 mg/kg iv Tramadol, Group C - 40 patients who received 1 µg/kg iv Clonidine.

Table 1: DEMOGRAPHIC DATA

	Group T (n=40)	Group C (n=40)	P Value
Age	27.72 ± 06.42	28.00 ± 06.02	0.11
Weight	57.90 ± 11.40	60.06 ± 11.20	0.08
SEX M/F	27/13	23/17	0.60
ASA GRADE 1/2	31/09	33/07	0.80

There is no significant difference in the age, sex and weight distribution between the two groups. Samples were atching by ASA grading also. Analysis was done by chi square test.(Table 1)

Table 2: HEART RATE (Beats Per Minute)

Time (in mins)	Group T (n=40)	Group C (n=40)	P Value
0	83.5 ± 6.0	83.2 ± 5.7	0.8
1	88.1 ± 8.4	89.2 ± 8.6	0.5
2	89.05 ± 9.22	93.3 ± 8.8	0.08
3	86.1 ± 9.2	90.0 ± 8.6	0.5
4	84.9 ± 10.1	85.0 ± 10.1	0.9
5	82.3 ± 9.3	82.0 ± 9.0	0.8
10	79.9 ± 9.1	79.2 ± 8.8	0.7
20	77.6 ± 8.3	77.8 ± 7.8	0.9
30	76.8 ± 7.5	76.2 ± 6.8	0.5
45	76.4 ± 6.7	75.4 ± 6.5	0.7
60	74.5 ± 7.0	74.8 ± 6.3	0.6

There is no statistically significant difference in HR between the two groups. Analysis was done by independent "t" test. The two groups maintained heart rate within 15% of basal value. (Table 2)

Table 3: SYSTOLIC BLOOD PRESSURE (mmHg)

Time (in mins)	Group T (n=40)	Group C (n=40)	P Value
0	122.4 ± 12.3	122.3 ± 13.3	0.9
1	129.6 ± 13.1	129.2 ± 14.2	0.9
2	127.3 ± 12.4	127.9 ± 12.8	0.8
3	124.2 ± 13.1	125.3 ± 13.0	0.7
4	120.0 ± 11.1	121.4 ± 10.9	0.5
5	118.7 ± 10.8	119.7 ± 10.9	0.6
10	117.9 ± 11.4	119.7 ± 11.7	0.4
20	119.6 ± 9.7	120.7 ± 10.1	0.6
30	120.9 ± 8.2	120.9 ± 8.7	0.9
45	120.1 ± 9.9	120.8 ± 10.4	0.7
60	119.3 ± 9.5	119.5 ± 10.2	0.9

There is no statistically significant difference in SBP among the two groups. Analysis was done by independent "t" test. The two groups maintained SBP within 15% of basal value. (Table 3)

Table 4: DIASTOLIC BLOOD PRESSURE (mmHg)

Time (in mins)	Group T (n=40)	Group C (n=40)	P Value
0	74.1 ± 7.5	74.1 ± 7.7	0.9
1	74.0 ± 5.5	73.9 ± 5.4	0.9
2	72.4 ± 5.6	73.1 ± 4.8	0.5
3	72.0 ± 5.1	71.6 ± 5.3	0.5
4	71.6 ± 5.5	71.6 ± 5.8	0.7
5	72.7 ± 5.9	72.6 ± 6.3	0.9
10	71.4 ± 5.5	71.6 ± 5.5	0.9
20	71.3 ± 6.3	70.7 ± 6.4	0.8
30	73.7 ± 5.7	73.3 ± 5.7	0.6
45	74.4 ± 5.5	74.2 ± 5.8	0.7
60	76.8 ± 5.8	76.9 ± 5.8	0.9

There's no statistically significant difference in DBP in the two groups. Analysis was done by independent "t" test. The two groups maintained DBP within 15% of basal value. (Table 4)

Table 5: TIME TO CONTROL SHIVERING (in minutes)

Group T (n=40)	Group C (n=40)	P
4.58 ± 0.59	8.02 ± 5.15	0.018*

P value is significant for the Tramadol group for stopping shivering. Tramadol has significant advantage over Clonidine for stopping shivering. Analysis was done by independent "t" test. (Table 5)

Table 6: RAMSAY'S SEDATION SCORING

Time (in mins)	Group T (n=40)	Group C (n=40)	P Value
0	2	2	
1	2	2	
2	2	2	
3	2	2	
4	2	2	
5	2	2.1 ± 0.03	0.02*
10	2	2.1 ± 0.30	0.04*
20	2	2	
30	2	2	
45	2	2	
60	2	2	

Sedation characteristics are significant at 5 minutes and 10 minutes for Clonidine. Clonidine causes more sedation Tramadol at 5 and 10 minutes. Analysis was done by independent "t" test. (Table 6)

Table 7: CONTROL OF SHIVERING

Time (in mins)	Group T (n=40)	Group C (n=40)	P Value
1	0	0	
2	0	0	
3	5 (12.5%)	2 (5%)	0.216
4	15 (37.5%)	9 (22.5%)	0.111
5	40 (100%)	21 (52.5%)	0.000*
10	40 (100%)	34 (85%)	0.013*
20	40(100%)	40 (100%)	
30	40 (100%)	35 (87.5%)	0.027*
45	35 (87.5%)	31(77.5 %)	0.189
60	40 (100%)	40(100%)	

P value is significant at 5 ,10 and 30 mins. Tramadol has significant advantage over Clonidine for stopping shivering early ie., at 5 and 10 minutes post shivering. Also it is useful for preventing an early recurrence at 30 minutes. Analysis done by Fischer exact test. (Table 7)

Table 8: MEAN TEMPERATURE (centigrade)

Time (in mins)	Group T (n=40)	Group C (n=40)	P Value
0	36.02 ± 0.19	36.08 ± 0.20	0.8
1	35.91 ± 0.17	35.90 ± 0.16	0.7
2	35.89 ± 0.14	35.88 ± 0.13	0.7
3	35.96 ± 0.14	35.95 ± 0.13	0.7
4	35.99 ± 0.12	35.97 ± 0.11	0.6
5	36.02 ± 0.14	36.01 ± 0.14	0.7
10	36.03 ± 0.14	36.02 ± 0.13	0.6
20	36.03 ± 0.14	36.01 ± 0.13	0.6
30	36.03 ± 0.14	36.01 ± 0.13	0.6
45	36.01 ± 0.12	36.01 ± 0.11	0.8
60	36.02 ± 0.15	36.01 ± 0.14	0.7

There is no statistically significant difference in temperature between the two groups. Analysis done by independent "t" Test. (Table 7)

Table 9: POST DRUG NAUSEA/VOMITING

Nausea / Vomiting	Group T	Group C	Total
Yes	5(12.5%)	2(5%)	7(8.75%)
No	35 (85.5%)	38(95%)	73 (91.25%)
Total	40(100%)	40(100%)	80(100%)

P=0.0936. There is no statistically significant difference in nausea/vomiting between the two groups. Analysis done by chi-square test. (Table 8)

4.DISCUSSION

Spinal anaesthesia is a safe and popular technique used world over for various surgeries. Spinal anaesthesia is a type of central neuraxial blockade, the other commonly used technique being epidural anaesthesia. The incidence of shivering in patients receiving regional anaesthesia is 19%-33%.[2,3] Shivering continues to be a common problem faced by the anaesthesiologist during intra operative and post operative periods following spinal anaesthesia. Unfortunately, there is no gold standard drug or definitive strategy drawn in management of this commonly encountered problem. Shivering is a very unpleasant experience for the patients receiving comforts of modern anaesthesia. At times it is described as a sensation worse than surgical pain. It is physiologically stressful; it increases oxygen consumption, which may go up by 100-600%. It increases intra ocular and intracranial pressures. It interferes with routine monitoring like ECG, pulse oxymeter and NIBP. It causes tension on suture lines. Shivering is detrimental to patients with low cardio respiratory reserve. It is uncomfortable to the patients as well as to the operating room personnel, especially during regional anaesthesia.[4,10,11] The exact mechanism of development of post anaesthesia shivering is not known. Many hypothesis like, perioperative heat loss, stress, the direct effect of certain anaesthetics (cold drug instillation), cold iv fluids, hypercapnia and hypoxia, uninhibited spinal reflexes, pain, early recovery of spinal reflex activity and sympathetic over activity.[5,6] Many physical methods like, active and passive warming systems, warming of inspired air, warming systems for IV fluids, blood and its products are tried in many studies, these methods require use of specialised equipment, which is not economically feasible and practical in all clinical settings.[7] Pharmacological methods are cost effective when compared to physical methods. There is no single gold standard drug for treatment of shivering. Many drugs like, Pethidine, Doxapram, Clonidine, Ketanserin, Propofol, Physostigmine, Nefopam, Alfentanil and Sufentanil are tried with success rates ranging from 30-95%.[7] Tramadol and clonidine are commonly studied drugs. Clonidine is associated side effects like bradycardia and hypotension, and tramadol is associated with nausea and vomiting and respiratory depression.[17,18] In the present study, the factors that influence the occurrence of shivering, like temperature of IV fluids and drugs, were not tightly controlled, but this should not affect the validity of our study because the present study is focused on response to treatment used rather than incidence of shivering; and by randomization, both groups were subjected to similar degrees of influence of these factors. We compared the efficacy of clonidine and tramadol for treatment of shivering after spinal anaesthesia in patients undergoing various surgeries. A limitation of this study is that we could not measure the core body temperature. For measurement of core body temperature, the probe needs to be put in the oesophagus or near the tympanic membrane. Both these are uncomfortable and unacceptable who has been given spinal anaesthesia. Rectal temperature monitoring was a possibility but was not tried. Clonidine is a centrally acting selective α_2 adrenoceptor agonist, with antihypertensive, sedative, analgesic and anti-shivering properties. The anti-shivering effects of alpha (α) adrenoceptor agonists are mediated by binding to α_2 receptors mainly the α_{2b} receptors that mediate vasoconstriction and the anti-shivering effect.[19] In addition clonidine has hypothalamic thermoregulatory effects,[16] as it may exert an inhibitory action on the hypothalamus, by decreasing the nor-adrenaline synaptic release through α_2

receptors located at the pre-synaptic nerve terminals, thus contributing to its anti-shivering effect.[20] At the spinal cord level, it activates the α_2 adrenoreceptors and release of dynorphine, norepinephrine and acetylcholine.[21] The depressor effects of these neurotransmitters at the dorsal horn modulate cutaneous thermal inputs.[22] Clonidine is highly lipid-soluble and easily crosses the blood-brain barrier.[23] Due to these merits, interaction at the a2 adrenoreceptors at spinal and supraspinal sites occurs within the central nervous system.[24] Clonidine provides a significant reduction in the incidence of post-extradural shivering without clinically relevant adverse side effects.[13,14,15,29] Tramadol is a novel analgesic, it has Opioid effect mediated via the mu-receptor, with minimal effect on kappa and delta receptors. Tramadol inhibits 5- HT3 reuptake and promotes its release. It also inhibits synaptosomal noradernaline reuptake.[4] Tramadol also 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.[26,27,28] Tramadol has been used as an analgesic for postoperative pain and labor analgesia without any adverse effects on the mother or baby.[25]

CONCLUSION:

In our study shivering control occurred in both groups but Clonidine group had delayed control and early recurrence and Tramadol group had early control and late recurrence. Complications like nausea, vomitimg occurred in both groups but no significant difference. Tramadol was found to have less sedation than Clonidine. We conclude that iv Tramadol (1 mg/kg) is an ideal alternative to iv Clonidine (1 µg/kg) to control post spinal shivering.

5.REFERENCES

1. Ozaki M, Kurz A, Sessler DI, Lenhardt R, Schroeder M, Moayeri A, et al. Thermoregulatory thresholds during spinal and epidural Anaesthesia. Anesthesiology 1994;81:282-8.
2. C K Koay, W Y Chan and M K Chin; Shivering during regional anesthesia and its control with pethidine; Singapore Med J 1991; Vol 32:160-162
3. D.J. Buggy and A.W.A Crossley; Thermoregulation, mild peri-operative hypothermia and post-anaesthetic shivering. British Journal of Anaesthesia 2000 84(54):615-28
4. Bhatnagar S, Saxena A, Kannan TR, Punj J, Panigrohi M, Mishra S. Tramadol for postoperative shivering; a double blind comparison with Pethidine. Anaesthesia and Intensive Care 2001; 29: 149-54.
5. Katyal S, Tewari A. Shivering: Anesthetic Considerations. J Anaesth Clin Pharmacol 2002;18:363-76.
6. Sessler Daniel I. Temperature Monitoring. In: Millar RD, 5 th ed. Textbook of Anaesthesia. Churchill Livingstone Inc, New York, 1994. p. 1367-89.
7. Bhattacharya PK, Bhattacharya L, Jain RK, Agarwal RC. Post anaesthesia shivering (PAS): A Review. Indian Journal of Anaesthesia 2003; 47(2): 88-93
8. Shukla U, Malhotra K, Prabhakar T. A comparative study of the effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth 2011;55:242-6
9. Reddy VS, Chiruvella S. Clonidine versus tramadol for post spinal shivering during caesarean section: A randomized double blind clinical study. J Obstet Anaesth Crit Care 2011;1:26-9
10. Saha E, Ray M, Mukherjee G. Effect of Tramadol in prevention of postanaesthetic shivering following general anaesthesia for cholecystectomy. Indian J. Anaesth. 2005; 49 (3) : 208 – 212.
11. Atashkhoyi S, Negargar S .Effect of Tramadol for prevention of shivering after spinal anesthesia for caesarean section. Res.J.Biol.Sci.,2008 3(2):1365-1369.
12. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW,: The minimum effective dose of pethidine and doxapram in the treatment of postanesthetic shivering. Anesthesia, 1977;52(1):32-36
13. Capogna G1, Celleno D.: IV clonidine for post-extradural shivering in parturients: a preliminary study. Br J Anaesth. 1993 Aug;71(2):294-5.
14. Mercadante S, De Michele P, Letterio G, Pignataro A, Sapio M, Villari P. : Effect of clonidine on postpartum shivering after epidural analgesia: a randomized, controlled, double-blind study. J Pain Symptom Manage. 1994 Jul;9(5):294-7.
15. Sia S: I.v. clonidine prevents post-extradural shivering. Br J Anaesth. 1998 Aug;81(2):145-6.
16. Tewari A, Katyal S, Singh A, Garg S, Kaul TK, Narula N. Prophylaxis with oral clonidine prevents perioperative shivering in patients undergoing transurethral resection of prostate under subarachnoid blockade. Indian J Urol 2006; 22: 208-12.
17. Grond S, Sablotzki A .Clinical Pharmacology of Tramadol. Clin Pharmacokinet 2004; 43 (13)879-923
18. Chan A M H, Jacobus Ng K F, Tong E W N and Jan G S K. Control of shivering under regional anaesthesia in obstetric patients with Tramadol. Can J Anesth 1999; 46(3): 253-258.
19. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology 2000;93:1345-9.
20. Shen KZ, Surprenant A. Mechanism underlying presynaptic inhibition through α_2-adrenoceptors in guinea-pig submucosal neurons. J Physiol 1990;431:609-28.
21. Powell RM, Buggy DJ. Ondansetron given before induction of anaesthesia reduces shivering afer general anaesthesia. Anesth Analg 2000;90:1423-7.
22. Alojado ME, Ohta Y, Kemmotsu O. The effect of clonidine on the activity of neurons in the rats dorsal raphe nucleus in vitro. Anesth analg 1994;79:257-60.
23. Timmermans PB, Brands A, van Zwietan PA. Lipophilicity and brain disposition of clonidine and structurally related imidazolidines. Naunyn Schmiedeberg Arch Pharmacol 1977;300:217-26.

24. Klimecsha W, Tong C, Eisenach JC. Intrathecal alpha-2 adrenergic agonist stimulate acetylcholine and norepiriphrine release from the spinal cord dorsal horn in sheep. An in vivo microdialysis study. Anaesthesiology 1997;87:110-6.
25. Viegas OA, Khaw B, Rathnam SS. Tramadol in labour pain primiparous patient. A Prospective comparative clinical trial. Eur J Obstet Gynaecol Reprod Biol 1993;49:131-5
26. Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Post-anaesthetic shivering: A new look at tramadol. Anaesthesia 2002;57:387-403.
27. Tsai YC, Chi KS. A comparison of tramadol, amitryptyline and meperidine for post-epidural anaesthetic shivering in parturients. Anaesth Analg 2002;93:1288-92.
28. Bilotta F, Pietropaoli P, Sanita R, Liberatori G, Rosa G. Nefopam and tramadol for the prevention of shivering during neuraxial anaesthesia. Reg Anaesth Pain Med 2002;27:380-4.
29. Zavaherforoush F, Pipelzadelimto, Bagherybarma F. Comparison of clonidin, pethedin and Fentanyl for post- spinal anaesthesia shevering in elective caesarian sections. Armaghan Danesh Fall ?006;11:60-7.

*****