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A Clinical Study to Evaluate the Effects of Perioperative Oral Amantadine on Postoperative Pain and Requirement of Morphine in Total Abdominal Hysterectomy

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ABSTRACT

Most of the patients about to undergo a surgery are anxious about post operative pain. Evidence reveals that adequate control of post operative pain is achieved only in a minority of patients. Therefore the conquest of better pain management continues in our clinical practice. Preemptive analgesia can help control postoperative pain and decrease the postoperative analgesic requirements. In this randomised blind study, the analgesic and the opioid sparing effect of oral amantadine, which is a NMDA receptor antagonist was studied. 60 women undergoing abdominal hysterectomy were randomised into 2 groups of 30 each. One group received oral amantadine night before and 2 hour before surgery and the other received placebo at the same time. Postoperatively the patients were given Inj Morphine for pain whenever the VAS score was more than 4 and they were observed for 48hrs postoperatively. The results were statistically analysed and it was observed that the average time for the first dose of morphine was significantly more in Amantadine group. VAS score in the Amantadine group were significantly lower and there were no major adverse effects with amantadine.

KEYWORDS : Amantadine, Morphine, Preemptive analgesia, Postoperative pain, Central Sensitization

INTRODUCTION:

Pain has remained the most universal affliction of the human race since time immemorial. One of the most common concern of patients before surgery is the presence of post operative pain. Evidence sugges ts that less than half of patients who undergo surgery report adequate postoperative pain relief (1) Inadequately controlled pain negatively affects quality of life, function, and functional recovery, the risk of post-surgical complications, and the risk of persistent postsurgical pain (2).

The currently available opioid analgesics provide a good pain free postoperative period, promote early ambulation and decrease morbidity but all suffer from disadvantages like nausea, vomiting, pruritis, respiratory depression, urinary retention and drug dependence which restrict their use.

Preemptive analgesia refers to the administration of an analgesic treatment before the surgical

insult (incision) or tissue injury. The concept of preemptive analgesia is based on well-recognized pathophysiology of surgical pain, which includes peripheral and central sensitization.

The N-Methyl-D-Aspartate(NMDA) receptor plays an important role in the process of central sensitisation(3,4). The role of NMDA receptor in development of central sensitization, acute opioid tolerance and opioid induced hyperalgesia has led to renewed interest for their clinical use in humans(5-7) Ketamine and dextromethorphan have been studied extensively in this regard. Amantadine is used for the treatment of Parkinsons disease and as an antiviral agent. Evidence shows it to be a non competitive NMDA receptor antagonist (8, 9). Therefore, amantadine may be useful in decreasing pain and analgesic requirements.

AIM:

To study the analgesic efficacy of perioperative oral amantadine on postoperative pain after abdominal hysterectomy

MATERIAL AND METHODS:

The permission to conduct the study was taken from the hospital ethics committee. Patients coming to the hospital for Total Abdominal Hysterectomy were randomly allocated to 2 groups of 30 patients each. The randomisation code for the GroupA and Group C was held by an observer. All clinical persons involved in the study were blinded.

The inclusion criteria were females in the age group of 25-65yrs, American Society of Anaesthesiologists(ASA) physical status 1,2 and the body weight between 50-80kgs. The exclusion criteria included ASA class3, 4; patients with CNS, respiratory, cardiac, hepatic or renal dysfunction; previous allergies or adverse effect to amantadine or opioid analgesics and history of alcohol or drug dependence.

Patients in the amantadine group received amantadine in a dose of 200mg at 2000hrs on the evening before surgery and 200mg 2hr before surgery. Patients in the placebo group received placebo capsules at the same time as the patients in the amantadine group.

General anaesthesia was given to all the patients for the surgery. Premedication included Inj Glycopyrollate 0.2mg and Injection Fentanyl 2mcg/kg. The patients were induced with Inj Thiopentone 3-5mg/kg and paralysed with Inj Vecuronium 0.1mg/kg and intubated with endotracheal tube. The anaesthesia was maintained with oxygen, nitrous and isoflurane and the muscle relaxation was given as necessary. At the end of the surgery the patients were reversed with Inj Neostigmine 0.05mg/kg and Inj Glycopyrollate 0.01mg/kg. All standard monitoring was used.

Postoperative pain management: Whenever patient complained of pain beyond a VAS score of 4, a loading dose of morphine 50mcg/kg IV was given to the patient. If the patient continued to have pain further increments of 50mcg/kg were given every ten minutes until the patient felt comfortable.

Post operative the parameters recorded every hour included the degree of analgesia using Visual Analog Scale, time interval at which patient required analgesia, nausea and vomiting and any other adverse effects.

OBSERVATION AND RESULTS:

Demographic Profile: A total of 60 patients were included in the study. The mean age of patients was 50.43yrs in the Amantadine (A) group and 52.34yrs in the control (C) group. The mean weight in Group A was 59.54 kgs and in Group C was 56.33 kgs. Both these parameters were comparable in the groups as shown in Table 1

Table 1 (Comparison of Age and Weight in 2 groups)

	Group	N	Mean	Std Deviation	P value
Age	A	30	50.43	4.28	0.88
	C	30	52.34	4.44	
Weight	A	30	59.54	5.36	0.92
	C	30	56.33	5.19	

Time to first dose of morphine: The mean time to first dose of morphine after the surgery finished was 3.46hrs in Group A and 2.14hrs in Group C. This was statistically significant as shown in Table 2

Total postoperative morphine: The mean of total post operative morphine was 12.3mg in Group A and 16.7mg in Group C. The difference was statistically significant as shown in Table 2.

Table 2(Time to 1st dose of Morphine, total postoperative morphine)

	Group	N	Mean	Std deviation	P value
Time	A	30	3.46	0.89	0.000
	C	30	2.14	1.09	
Total Dose	A	30	12.30	2.53	0.000
	C	30	16.70	3.21	

Comparison of VAS scores: Comparison of VAS scores was made at different time points between the groups by Mann- Whitney test. They were significantly less at all time points in Group A except at 42 and 48hrs as shown in Table 3.

Table 3 (Comparison of VAS Scores at different time intervals)

	VA S3	VA S6	VA S12	VA S18	VA S24	VA S30	VA S36	VA S42	VA S48
Mann Whitney U	289	202	181	246	234	271	275.5	379.5	197
Wilcoxon W	754	667	646	711	699	736	740.5	844.5	662
Z	-2.54	-3.82	-4.20	-3.14	-3.46	-2.80	2.74	-1.12	-3.97
P value	0.011	0.000	0.000	0.002	0.001	0.005	0.006	0.259	0.243

DISCUSSION:

Intraoperative and postoperative noxious inputs may cause central sensitization, but analgesic interventions given before the noxious stimulus may attenuate or block sensitization and hence reduce pain (10). The concept of preemptive analgesia was put forward by Crile(11) and then by Wall(10) who suggested that the administration of opioids or local anaesthetics before surgery might reduce the C fibre induced injury barrage with incision, and thereby, the intensity of postoperative pain.

Perioperative administration of NMDA antagonists that is, before during and after surgery may be an ideal intervention to block the initiation and maintenance of central sensitization. Several studies have found that this intervention reduces postoperative hyperalgesia, pain and analgesic use however others have not found these effects.

Snijdelaar, Gideon Koren et al evaluated the effects of perioperative amantadine on postoperative pain and analgesic consumption. 24 patients scheduled to undergo radical prostatectomy were given oral amantadine before and after surgery in a randomised, double blind, placebo controlled manner. They concluded that perioperative oral amantadine reduced post operative opioid consumption by pharmacokinetic mechanics, although additional pharmacodynamic interactions may also be involved.(12)

Andre Gottschalk et al carried out a prospective, randomised clinical study to examine whether female patients undergoing elective abdominal hysterectomy experienced less postoperative pain when intravenous amantadine was applied in comparison with placebo before the start of the surgery. As there was no difference in postoperative pain or opioid consumption, they concluded that a preoperative dose of 200mg IV amantadine failed to enhance postoperative analgesia in patients undergoing elective abdominal hysterectomy.(13)

This is not surprising given the variability across studies in factors such as surgical procedure, extent and nature of tissue damage, duration of surgery, pharmacokinetics of agents tested, intraoperative and postoperative analgesia. Nonetheless, the weight of evidence suggests that preventing or minimising central sensitization reduces pain and analgesic requirements.

Therefore this double blind randomised controlled trial was undertaken to evaluate the efficacy of preoperative oral amantadine for postoperative pain relief and opioid sparing effect. We found an excellent analgesic effect of preoperative amantadine given night prior and two hours prior to the surgery. The Amantadine group had lower VAS scores at all the time points. The average time for first dose of rescue morphine was also increased post operatively. We didnot find any significant adverse effect due to amantadine.

CONCLUSION:

It is concluded that perioperative oral Amantadine provides good analgesic and opioid sparing effect in the post operative period. It increases the time to first postoperative dose of opioid and also decreases the total opioid requirement. There are no serious adverse effects associated with the use of oral amantadine.

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