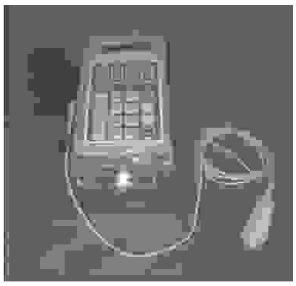
ORIGINAL PROF-1172

POST-OPERATIVE PAIN;

MULTI-MODAL ANALGESIA TECHNIQUE IS SUPERIOR TO CONVENTIONAL SINGLE ANALGESIA.



DR AZMAT RIAZ, MBBS, MCPS, FCPS
Consultant Anesthesiologist
PAF Hospital, Islamabad.

ABSTRACT... azmatrt@yahoo.com **Objectives:** To compare the efficacy of a multi-modal analgesic regime with conventional single drug analgesic therapy after total abdominal hysterectomy under general anaesthesia. **Design of Study:** Prospective, random clinical trial. **Setting:** A 250 bedded secondary care hospital. **Period:** From march 2006 to September 2006. **Material and Methods:** In this study, forty ASA 1-2 middle aged females presenting for elective total abdominal hysterectomy were randomized to receive multi modal pain treatment with oral celecoxib, intravenous tramadol, incisional bupivacaine and intramuscular diclofenac sodium until hospital discharge (Group I) or conventional therapy with intravenous nalbuphine peri and post-operatively (Group II). Both groups received general anaesthesia. Visual analog pain score was recorded in recovery room, then 4 hourly during the first 12 hr, and then 6 hourly for next 12 hours. Post-operative analgesia was managed with diclofenac sodium 75mg im and nalbuphine 10mg im every 6 hourly in respective groups. Request for additional analgesic was noted and dealt accordingly. Incidence of side effects and surgical complications were recorded. **Results:** In the recovery room only one patient of Group one (multi-modal group) (n=20) experienced severe pain as compared to 4 patients of group two 'single analgesic group (n=20) (5% vs.40%).In next 24 hours, pain score were considerably lower in group one as compared to group two. After 24 hours 15 patients had no pain on VRS as compared to 11 patients (75% vs. 55 %). Four patients of group two needed rescue analgesia while none of multi-modal group demanded it. Incidence respiratory depression, nausea and vomiting were also lower in multi-modal group. **Conclusion:** Multimodal analgesic regime is an effective tool in reducing the post-operative pain after major gynaecological surgery. By employing multimodal analgesic technique incidence of side effects like respiratory depression, nausea and vomiting were also reduced and patient satisfaction was more.

Key words: Multi-modal analgesia, COX-2 inhibitors, Tramadol, Nalbuphine, NSAIDs.

INTRODUCTION

Few sensations are as disturbing to the individual as that of pain. This is recognized by the International Association for the Study of Pain (IASP), which defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". The concept of multi-model analgesia (also known as balanced analgesia) is analogous to that of balanced anaesthesia. It suggests that a combination of opioid and no-opioid analgesic drugs will enhance the analgesic efficacy and reduce side-effects after surgery[1]. Despite their well known side effects[1] opioid analgesics remain the main therapies for moderate to severe pain after

surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used adjunctively in the management of pain after a variety of surgical procedures[2]. It is possible to block the development of pain by the use of a combination of different drugs acting at different sites: peripherally, on somatic and sympathetic nerves, at spinal cord level, and centrally. The advantages are that superior analgesia is achieved by a combination of drugs as well as their doses are reduced, thereby decreasing the incidence of side effects[3].

MATERIALS AND METHODS

After approval from hospital ethical committee, 40 ladies scheduled for elective total abdominal hysterectomy under general anaesthesia, were selected for the study. Study entry criteria included middle-aged ladies (45-70 years), ASA physical status 1 and 2, body weight of at least 50 kg and no more than 50% above ideal body weight, refusal for surgery under central blocks and ability to understand the pain assessment scales. Exclusion criteria included patients with ASA physical status 3 and above, emergency surgery, known allergy, sensitivity or contraindication to opioids and NSAIDS, history of bleeding disorders, peptic ulceration, use of anticoagulants, or suspected drug abuse. One day before the surgery, patients were examined in the pre-anaesthesia clinic.

They were explained the purpose, technique and risks of study and consent were taken. Patients were divided into two groups. After an overnight fast, both groups were given standard general anaesthesia; induction with propofol (1-2.5 mg/kg), intubation with atracurium (0.6 mg/kg), maintenance with oxygen, nitrous oxide and isoflurane (0.5-1%) and reversal with neostigmine and atropine. Group one (multi-model group)was given one capsule of celecoxib one hour before the surgery and tramadol 50 mg i.v 5 minutes before the surgery. At the end of surgery, incision was infiltrated with 0.25% 15ml bupivacaine, and diclofenac sodium 75mg was injected intramuscularly before reversal of anaesthesia. Group two (single analgesic group) was given nalbuphine 0.1 mg/kg, 5 minutes before start of surgery. A 4-point verbal rating scale (VRS), with 0=none, 1=mild, 2=moderate and 3=severe was used to evaluate pain intensity. In the recovery room, when patients gained full recovery (recovery score=10), first reading of pain score was taken. Then 4 hourly for first 12 hours and then 6 hourly for next 12 hours. For post-operative pain relief, group one was given 75 mg diclofenac sodium im 6 hourly and group two was given nalbuphine 10 mg im 6 hourly. Time to first analgesic request was recorded and dealt with additional analgesic of respective groups. Postoperative complications like nausea, vomiting, respiratory depression (resp rate < 6/min), itching, ilius, and wound hematoma were recorded.

RESULTS

Both groups were comparable in age, weight and duration of surgery. Postoperative Visual Analogue Pain Scores of Group one (multimodal group) were lower in the recovery room as compared to Single analgesic group (figure 1).Severe pain was present in only one patient, as compared to 4 patients (Table I).

Table-I. Demographic characteristics. Values are in mean (SD).

	Multi-modal group	Single analgesic group
Number (n)	20	20
Age (yrs)	49(10)	52(9)
Weight (kg)	77(22)	75(14)
Surgical time (min)	121(42)	115(41)

In recovery room no of total pain free patients was 5 while none of group two was in total pain free state. Post-operatively in 24 hours, pain score were considerably lower in group one as compared to group two (figures 2 and 3).After 24 hours 15 patients had no pain on VRS as compared to 11 patients (75% vs. 55 %) (figure 4).Rescue analgesia was not demanded by any patient of group one while 4 patients of group two needed it (table II).Respiratory depression (respiratory rate <6/min) was not seen in any patient of group one as compared to one patient in group two (table III).Incidence of nausea and vomiting was also lower in group one (15% vs. 40%) and (5% vs. 10%) respectively (table III).

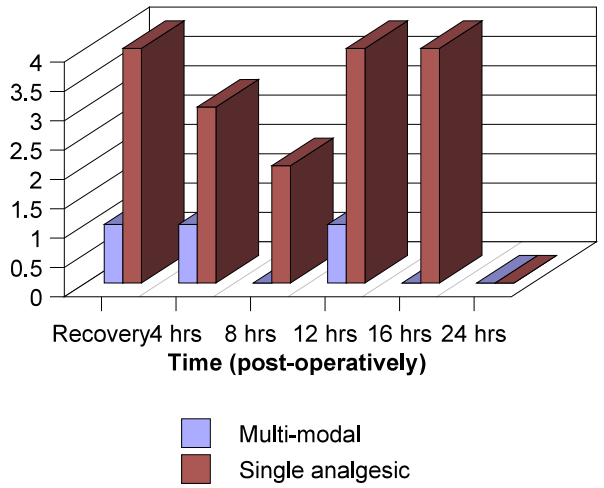
Table-II. Pain scores of both groups in the recovery room and 24 hours post-operatively. Values are in numbers (n) and percentages (%)

	Multimodal group n=20	Single analgesic group n=20
Recovery room		
Severe	1 (5)	4 (20)
Moderate	4 (20)	5 (25)
Mild	9 (45)	11 (55)
None	5 (25)	0 (-)
4 hours after surgery		
Severe	1(5)	3 (15)
Moderate	2 (10)	4 (20)
Mild	5 (25)	9 (45)
None	12 (60)	4 (20)
8 hours after surgery		
Severe	0 (-)	2 (10)
Moderate	2 (10)	3 (15)
Mild	4 (20)	5 (25)
None	14 (70)	10 (50)
12 hours after surgery		
Severe	1 (5)	4 (20)
Moderate	2 (10)	4 (20)
Mild	4 (20)	9 (45)
None	13(65)	3 (15)
18 hours after surgery		
Severe	0 (-)	2 (10)
Moderate	1 (5)	4 (20)
Mild	5 (25)	9 (45)
None	14 (70)	5 (25)
24 hours after surgery		
Severe	0 (-)	0 (-)
Moderate	1 (5)	2 (10)
Mild	4 (20)	7 (35)
None	15 (75)	11 (55)

Table-III. Incidence of side effects and need of rescue analgesia

Side effects	Multimodal group	Single analgesic group
Rescue analgesia	0 (-)	4 (20%)
Nausea	3 (15%)	8 (40%)
Vomiting	1 (5%)	2 (10%)
Respiratory depression	0 (-)	1 (5%)
Urinary retention	1 (5%)	1 (5%)
Itching	0 (-)	0 (-)
Wound hematoma	0 (-)	0 (-)

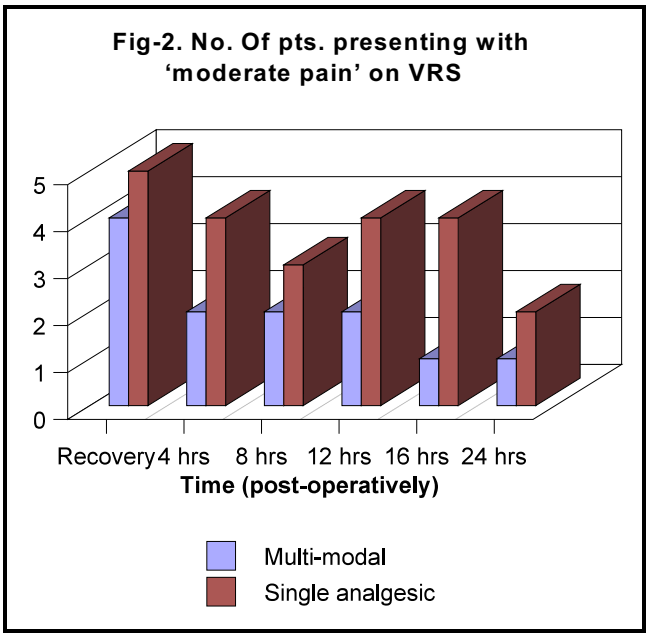
Fig-1. No. Of pts. presenting with 'severe pain'

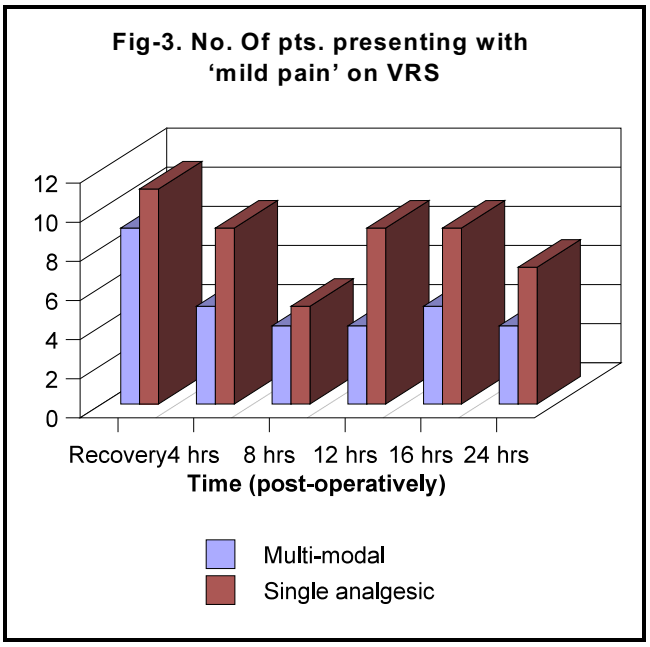


DISCUSSION

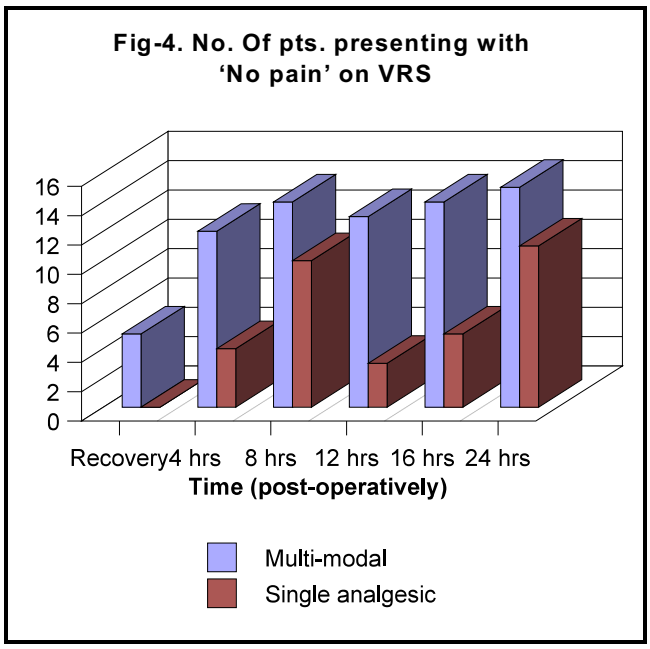
Pain receptors, also called as nociceptors are distributed with varying densities in different tissues. They may be stimulated by mechanical damage, extremes of temperature, or by irritating chemical substances. When the pain receptors in peripheral tissues (such as skin) are stimulated, the nociceptive (pain) impulses are transmitted to the CNS by two distinct types of neurons - the A-delta and C nerve fibres. When nociceptors are activated by the noxious stimuli that accompany tissue damage or infection, a regional injury response occurs in

the periphery. Chemical substances and enzymes are released from the damaged tissues, increasing the transduction of painful stimuli.





Prostanoids (prostaglandins, leukotrienes and hydroxyacids) are products of the arachidonic acid pathway and are major mediators of the hyperalgesia that accompanies inflammation. Prostaglandins (PGs) and leukotrienes cause sensitization of the peripheral receptors, reducing their activation threshold and increasing their responsiveness to other stimuli Celecoxib is a NSAID which selectively inhibits cyclooxygenase (COX-2).



It produces good analgesia and is devoid of most gastrointestinal side effects. Renal and hepatic toxicity remains the main side effects. In normal doses it doesn't affect platelet functions. NSAIDs are not sufficiently effective as the sole analgesic agents after major surgery. But they offer certain advantage, like decreased opioid requirements, significant reductions in opioid side-effects and enhancement of quality of opioid based analgesia. By reducing PG synthesis, cyclo-oxygenase inhibitors block the nociceptive response to endogenous mediators of inflammation, with the effect being greatest in tissues that have been subjected to injury and trauma [4].NSAIDs represent diverse chemical entities, but their common mechanism of action is inhibition of this PG-mediated sensitization of nociceptors to chemical and mechanical irritants[5]. Moreover, membrane stabilization by NSAIDs may account for the decrease in PG release seen at concentrations insufficient for effective inhibition of cyclo-oxygenase[6]. Glucocorticoids, tricyclic antidepressants, anti-arrhythmics and local anesthetics

may work by a similar mechanism, as all are considered to possess membrane-stabilizing effects. Giving oral celecoxib 2 hours before surgery is part of preemptive analgesic technique. The physiological basis of preemptive analgesia is complex and involves modification of the pain pathways[7]. The pharmacological modalities available may modify the physiological responses at various levels. Effective preemptive analgesic techniques require multi-modal interception of nociceptive input[8], increasing threshold for nociception, and blocking or decreasing nociceptor receptor activation. To what extent the central action of NSAIDs contributes to the analgesic effect of systemically administered NSAIDs is unknown[9]. It is apparent that in addition to their effects on PG synthesis, certain NSAIDs also affect the synthesis and activity of other neuroactive substances, such as 5-HT, kynurenic acid and polyamines, thought to play important roles in the processing of nociceptive impulses in the dorsal horn. Buggy et al[10]. compared the preemptive analgesic effects of diclofenac in a randomized, double-blind study of 40 healthy female patients undergoing laparoscopic tubal ligation. The treatment group received in diclofenac one hour before operation and the control group patients received in diclofenac immediately after surgery. The treatment group had lower pain scores at 30 min, one, three and six hours and had a longer latent period until they requested the first dose of morphine.

Tramadol, although comes under the classification of opioids, but its mode of action is three fold[11]. It is a phenylpiperidine analogue of codeine and is a recemic mixture of two enantiomers. It binds to and activates the opioid receptors with a 20-fold preference for u receptors. This action is weak but is that of a full agonist. It also inhibits the neuronal uptake of nor-epinephrine, potentates the release of serotonin and causes descending inhibition of nociception. In therapeutic doses, the effects on ventilation and cardiovascular system are clinically insignificant[12]. Side-effects seen in the clinical use include nausea, dry mouth, sweating, vomiting and urinary retention. Pharmacologic agents such as NSAIDs, opioids, and NMDA (N-methyl-D-aspartate) - and alpha-2-receptor antagonists, especially when used in combination, act synergistically to decrease postoperative pain.

At the spinal cord, modulation of afferent input can be accomplished by decreasing neurotransmitter release, by blocking the postsynaptic receptors (thereby blocking the effects of the neurotransmitters), or by activating inhibitory pathways. Opioid receptors are a key site of analgesia production and recent studies indicate that spinal opioid systems can be enhanced or reduced under different circumstances[13]. The lamina I and the substantia gelatinosa in the dorsal horn, the zones in which C-fibres terminate, have the highest concentrations of opioid receptors in the spinal cord. The majority of the mu-receptors in the spinal cord are found presynaptically on the afferent nociceptive terminals[14]. Opioids that are mu and/or delta agonists cause a reduced release from C-fibres of primary afferent neurotransmitters (substance P and glutamate). Opioids also inhibit the release of CGRP. The predominance of presynaptic opioid receptors on C fibres, as opposed to A-fiber terminals, accounts for the selective effect of spinal opioids on noxious evoked activity[15]. Richmond et al[16] performed a randomized, double-blind study comparing the effects of parenteral morphine given before or after total abdominal hysterectomy in 60 patients. Morphine 10 mg was given either intramuscularly one hour preoperatively, intravenously at induction of anesthesia, or intravenously at closure of the peritoneum. Morphine consumption was significantly reduced in the second group for 24 hr postoperatively compared with the last group. Pain sensitivity around the wound was reduced in both preoperative treatment groups compared with the last group. The authors concluded that preemptive analgesia with i.v morphine prevented the establishment of central sensitization during surgery, and reduced the postoperative pain, analgesic requirements, and secondary hyperalgesia. Opioids also act peripherally as analgesic agents[17]. Mu receptor agonists prevent the nociceptor sensitization induced by inflammatory mediators, such as prostaglandin E_2[18].Delta and kappa receptors are thought to be located on the sympathetic nerves and to mediate analgesia peripherally by blocking bradykinin-induced release of nociceptor sensitizing agents from nerve endings. The best approach is probably to administer a number of analgesic agents and

techniques in combination, each of which decreases nociception by working on a different limb of the pain pathway and at different sites. Such an approach will allow synergism between the different medications while decreasing the risk of toxicity by limiting the dose of each of the individual agents.

CONCLUSION

Pain is the main fear of patient related to surgery. Anesthesiologist has to play the vital role in keeping the patient in a pain free state. The above study showed that multimodal analgesic technique is very effective in reducing the pain associated with major gynaecological surgery. It not only effectively reduced the post-operative pain but some side effects like nausea and vomiting were also reduced. Although this technique requires slightly more effort on the part of anesthesiologist, but the reward is a pain free and satisfied patient.

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