Multimodal Analgesia Prolongs Duration of Postoperative Analgesia and Decreases Postoperative Pain Intensity in Short Surgical Procedures: a Randomized Controlled Trial.

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ABSTRACT

Background: We examined the effect of preoperative combination of different analgesics and the role of each individual analgesic compared to control regarding postoperative pain,
Methods: patients were randomly allocated into either control; multiple treatment, perfalgan, opioid and voltaren group. The time for first request for analgesia and visual analogue score were compared by analysis of variance and tuckey Kramer test.
Results: There was a main effect of treatment p>0.0001 in favor of multi-analgesia and opioid groups. Multi-analgesia group was better than opioid group p=0.016. There was a little improvement with paracetamol (perfalgan) but no effect of voltaren on duration of analgesia nevertheless;both have reduced VAS relative to control.
Conclusion: Combination ofnon-opioid analgesicsDiclofenac Na (voltaren), Paracetamol (perfalgan) with low dose morphine and dexamethasone have greatly prolonged duration of analgesia and reduced pain intensity without displaying notable side effects.

***Keywords**:* pain, postoperative; multimodal analgesia; analgesics nonopioid, diclofenac Na; analgesics non-opioid, paracetamol; analgesics opioid, morphine; dexamethasone.

INTRODUCTION

Management of post-operative pain is essential to reduce morbidity and enhance convalescence [1].

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Despite opioids play an important role in management of postoperative pain, high doses of opioids are associated with many adverse effects such as; nausea, vomiting pruritus, constipation ,urine retention and respiratory depression[2,3] .

There is a growing body of evidence that the use of multiple analgesics can have a substantial effect in reducing postoperative pain and its consequences ([4,5,6]**.** Furthermore, combination of different analgesic drugs reduces dosage of each agent therefore, decreasing adverse effects of each individual drug [7].

However, there is no universal pain control protocol that has been shown to be effective and in the meantime side effect-free.

The ideal dosage of each analgesic in an analgesic mixture and the role of each individual analgesic among multiple analgesics working on different receptor sites remain elusive.

Nonstreoidal anti-inflammatory drugs (NSAIDs) have been shown to decrease pain, opioid consumption and enhance recovery after surgery [8,9].

However, their role in postoperative pain relive as sole analgesics and effects of their combination in analgesic mixture is not clear.

We hypothesized that the combination of least therapeutic doses (as recommended by manufacturer) of cox1, cox2, cox3 analgesics plus dexamethasone would reduce opioid dosage by 50% yet attaining the same analgesic effect without notable side effects.

PATIENTS AND METHODS

The present study is a randomized double-blinded controlled study. After approval of the ethical committee and anesthesia department of Faculty of Medicine, Menuofiya University, and a written consent was obtained from each patient, 100 ASA I and II patients of both sexes were randomly allocated into one of five treatment groups depending on the type of analgesic drugs used. Randomization was generated by the computer with the help of an on line true random number generator program. Investigators and outcome assessors were blinded to group assignment by pharmacy-encoded syringes. The control group received fentanyl citrate 1 mcg/kg intravenously(Janssen Cilage) plus normal saline immediately before induction of anesthesia. The opioid group received fentanyl 1 mcg/kgIV in addition to morphine 0.1 mg/kg(Bodene PTY) in normal saline immediately before induction of anesthesia. The paracetamol group received fentanyl 1 mcg/kg IV in addition to one gram Paracetamol (perfalgan, Bristol MeyersSquib) in saline by IVinfusion immediately before induction of anesthesia. The multiple analgesic group received fentanyl 1 mcg/kg IV in addition to paracetamol one gram, diclofenac NA 75 mg (Voltaren, Novartis), morphine 0.05 mg/kg and dexamethasone 8 mg IV (Dexamethasone phosphate, Epico)in saline by IV infusion immediately before anesthesia induction. The voltarengroup received fentanyl 1 mcg/kg IV plus voltaren 75 mg in normal saline by IV infusion of voltaren immediately before anesthesia induction.

Anesthesia was induced by propofol 2 mg/kg, endo-tracheal intubation was facilitated by atracurium 0.5mg/kg and anesthesia was maintained by sevoflurane 2% O2 50% air 50% in all patient groups.

NIBP, Spo2, end tidal CO_2, O_2 N_2O % and anesthetic concentration were monitored throughout the procedure.

Pulse, NIBP, Spo2 were recorded before induction, after intubation, 15 minutes and 30 minutes after induction.

The patients were extubated and kept in recovery for 3 hours where the first request for analgesia and visual analogue score were recorded by an experimenter who was blinded to the treatment groups. Visual analogue score was estimated on 10 cm scale ranging from zero (no pain) to 10 (the worst imaginable pain).

Patients that spent 3 hours without requesting analgesia their time was recorded 180 minutes and pain score is zero.

On first request for analgesia andafter estimating the pain score rescue analgesic pethidine 25 mg, IV was given and repeated if not satisfactory. The total dose for rescue analgesic was recorded for every patient. If a patient does not request analgesia for 180 minutes (3 hours),the consumption dose was considered zero.

STATISTICAL ANALYSIS

Power analysis was done based on pilot study comparing time for first request for analgesia as a primary determinant of sample size. With á =0.05 revealed that a sample size of ten is required to generate power of 95%, we doubled the sample size to give fair chance to all groups.

Duration of first request for Analgesia was analyzed by (ANOVA) analysis of variance, the tuckey Kramer adjustment for multiple comparisons was applied to pair wise comparisons. The visual analogue scores (pain intensity) were compared by Kruskal- Wallis Multiple pair wise comparisons using the Steel-Dwass-Critchlow-Fligner procedure. Comparisons between opioid group and multimodal group was analyzed using student t test after exclusion of other groups using the XL stat 2013.

P value < 0.05 was considered significant.

RESULTS

The hundred patients underwent different elective surgical procedures, laparoscopic cholecystectomy 50 patients, hernia repair36 patients, hemorroidectomy 14 patients(table 1). The surgery time ranged from 30 minutes to 65 minutes.

Table 1: Number of patients in each group in relation to the type of surgery.

Group	Control	Opioid	Multi	Voltaren	Perf	Total
Lap chole	8	11	8	11	12	50
Hernia	8	6	9	7	6	36
piles	4	3	3	2	2	14
Total	20	20	20	20	20	100

Distribution of surgical procedures in different groups.
Lap chole= Laparoscopic cholecystectomy, multi= multiple analgesia group, perf= perfalgan group.

By comparing physiological variables there was no statistical difference in age, pulse, Blood pressure, Oxygen saturation (SPO_2) or body weight among treatment groups.

In addition, there was no statistical difference in duration of surgical procedures (Table2).

Table 2: Physiological variables; there is no statistical difference among groups.

Control	Multi	Opioid	Perfalgan	Voltaren	
No	20	20	20	20	20
Age	38±11	39±9	35±10	38±10	38±10
BW	80±9	81±12	81±9	79±9	80±12
Preoperative					
Pulse	85±12	86±18	85±19	78±15	83±15
SBP	132±14	142±13	135±13	133±15	131±11
DBP	83±11	85±11	84±9	80±11	82±8
After anesthesia					
Pulse	84±16	83±15	85±16	86±14	84±14
SBP	116±16	117±17	112±14	112±22	104±14
DBP	72±13	70±15	62±14	68±17	64±10
After15 minutes					
Pulse	75±13	80±17	73±12	73±15	72±13
SBP	110±18	101±20	106±16	105±15	101±13
DBP	71±14	62±19	65±17	64±12	65±11
After 30 minutes					
Pulse	77±15	76±17	73±12	77±15	75±11
SBP	114±16	110±20	110±17	111±17	108±15
DBp	75±15	68±17	66±14	68±16	69±11
Duration of surgery	44±8	46±9	45±9	42±9	45±9

Values presented as mean± Standard deviation.Multi= multiple analgesia group; No=number; SBP=systolic blood pressure; DBp=diastolic blood pressure, BW=body weight.

Comparing first request for analgesia among treatment groups revealed main effect of treatment in delaying postoperative pain p> 0.0001. The multiple analgesic group

has significantly prolonged analgesia time 155±30minutes than control group 76±16 minutes p value >0.0001(Table three, Figure 1).

Table 3: first request for analgesia and pain score

	First request	p value	pain score	p value
Control	73±14		7.6±1	
Multiple analgesia	155±30	>0.0001* 1.9±2	<0.0001*	
Opioid	125±38	>0.0001* 4.3±2	<0.000*	
Perfalgan	96±18	0.018*5.25±2	0.000*	
Voltaren	76±16	0.934	6 ±1.7	0.01*

Values presented as mean± Standard deviation. *= significant

Represents primary outcome variables; first request for analgesia and visual analogue pain score among groups. ANOVA revealed better analgesia duration of multi-analgesia group, opioid group and perfalgan group relative to control. Voltaren showed no effect of duration of analgesia. Kruskal- Wallis Multiple pair wise comparisons revealed better pain scores in multiple analgesia, opioid, perfalgan and voltaren relative to control.

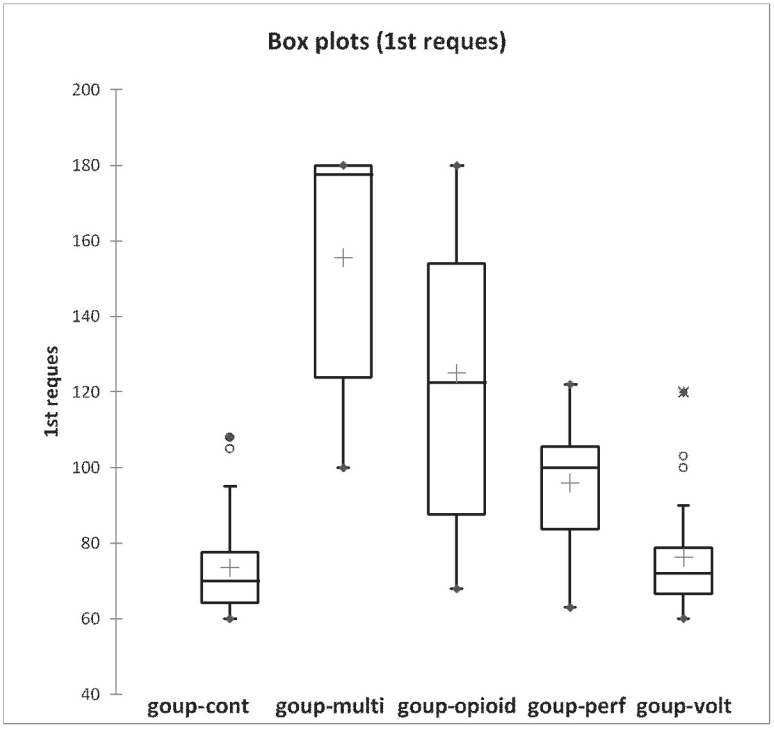

Fig. 1: Comparing time for first request for analgesia among groups

The effect of treatment on duration of analgesia revealed substantial prolongation of analgesia in multimodal group155±30 p value >0.0001 in comparison to control group 73±14. Both opioid and perfalgan treatment showed a significant effect in comparison to control P>0.0001 and = 0.018 respectively. Cont=control, multi= multiple analgesia, perf = perfalgan Volt = voltaren.

In addition opioid group prolonged analgesia time 125±38 compared to control group 73±14 minutes p value >0.0001.

There was an effect with treatment with perfalgan 94.4±18 p value = 0.018 but no effect with voltarin 74.7±17.3 minutes p value= 0.934.

Comparison between multiple analgesia group and opioid group after exclusion of other groups using student t test have revealed better duration of analgesia in multiple analgesic group than in opioid group p value= 0.016 .

The effect of treatment on intensity of postoperative painComparing, VAS among groups have revealed the best analgesia quality with lowest pain scores in multiple analgesia group 1.9±2 compared to control group which yielded the most severe pain 7.6±1 p <0.0001.Multiple analgesia group resulted in better pain relief with lower pain scores than opioid, perfalgan and voltaren p value=0.018, 0.001, <0.0001 respectively.

Treatment with opioids or perfalgan or voltarin have resulted in intermediate pain intensities 4.3±2, 5.3±2 and 6±1.7 respectively (Table 3 Figure 2).

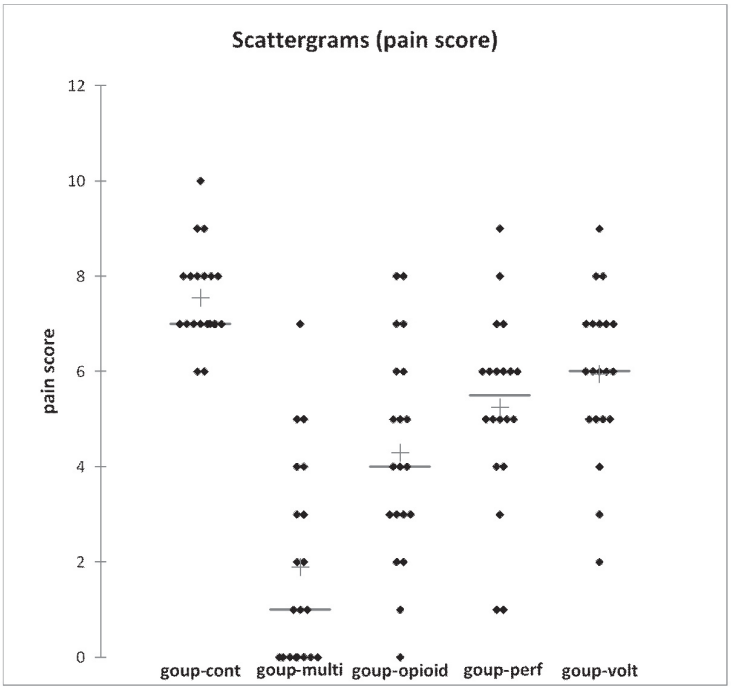

Fig. 2: Pain Scores

The effect of treatment on intensity of pain by comparing visual analogue pain score among treatment groups. Visual Analogue score raging from zero to ten value. Combination of different analgesics resulted in the best reduction in pain intensity p value<0.0001.other groups provided intermediate reduction of VAS relative to control. Cont=control, multi= multiple analgesia, perf=perfalgan Volt=voltaren.

Most patients with pain scores four and below showed pain relief with single dose of 25 mg pethidine; whereas patients whom pain score of 6 and above received more than one increment of 25 mg to attain pain relief.

Side effects. Two cases of vomiting and one case of pruritus were recorded in opioid group No other side effects were noticedduring the period of study.

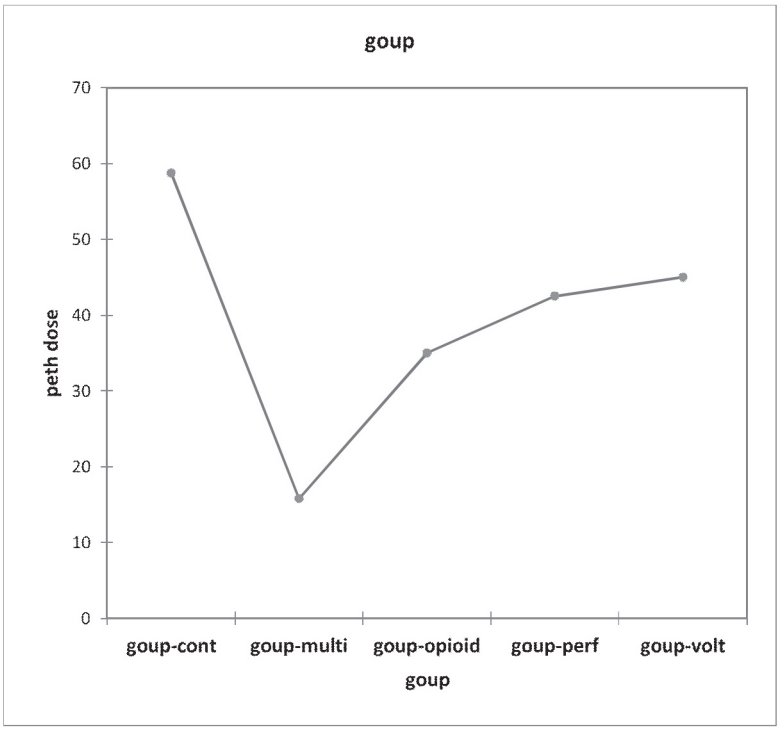

Fig.3: Rescue Analgesic Dosage
Reveals effect of different group pretreatment on rescue analgesic dosage
Pretreatment with multiple analgesic regimen has strongly reduced pethidine dosage 16.3±14 Compared to control group 59±14 p value <0.0001. Peth dose=pethidine dosage on first request. Multi= multiple analgesia group. Cont. =control, perf= perfalgan
Volt=voltaren.

DISCUSSION

Acute postoperative pain is a predictable response. Recent research has demonstrated that untreated acute postoperative pain can lead to chronic persistent pain [10,11] Faster recovery, reduced hospital stay, and decreased length of convalescence can occur if multimodal analgesia is combined with a rehabilitation program that is multidisciplinary and multimodal [12].

Lack of postoperative pain control may lead to many adverse effects including respiratory, cardiovascular, gastrointestinal, urinary, endocrinological systems, as well as in patient's metabolisms and mentality [13].

We have studied effects of treatments in a variety of short surgical procedures because of relevance of this to ambulatory anesthesia in which pain control is an essential feature for prompt discharge.

The main finding in the current study is that preoperative administration of combined various analgesics not only prolonged the duration of postoperative analgesia but also improved the pain intensity as well without displaying notable side effects regarding the number of treated patients. This is consistent with recent reports who demonstrated superiority of multimodal over single agent analgesia[14,15,16,17]. Surprisingly combination of morphine in lower dosage with diclofenac NA, paractamol and dexamethasone have improved postoperative analgesia and ameliorated postoperative pain in comparison with high(double) opioid dosage without displaying notable side effects. Therefore, the NSAID, Paracetamol and dexamethasone have provided synergism to low dose morphine, which have exceeded doubling morphine dosage in both quantity and quality of pain control. The mechanism of this interaction warrants further investigation.

Treatment with perfalgan have improved the duration of analgesia relative to control, this is consistent with Gray et al[18] who reported improvement with paracetamol treatment.

NSAID (Diclofenac Na) treatment failed to improve duration of postoperative analgesia relative to control p=0.934. This is inconsistent with Cassinelli et, al. and Wong *et al* [19,20] who demonstrated improvement with NSAID treatment. This difference in results may be due to the use of different NSAID Ketorlac in their studies rather than diclofenac Na in ours.

The question of why improvement occurred with paracetamol but not diclofenac remains to be determined. It is possible that different mechanisms of action central Cox 3of paracetamol versus Cox 1 and2 of diclofenac and its effects in early postoperative period have accounted for the difference.

In accordance with Miranda *et, al* [21]; Tarkkila and Saarnivaara [22] Both Voltaren and Perfalgan when used alone have improved pain intensity in the used doses as noted by significant reduction in VAS.

Lack of long-term follow up represents a limitation of the present study in defining the role of this combination in prevention of development of chronic pain.

Pain involves multiple mechanisms that ideally require treatment using a multimodal analgesic technique [15].

NSAIDs are known to achieve pain relief by their effect on COX-1 and COX2; these agents possess both analgesic and anti-inflammatory properties by inhibiting prostaglandin synthesis [23]. Paracetamol has antipyretic and analgesic properties, but it is devoid of anti-inflammatory effects. It has an inhibitory action on central COX-2 and COX-3 enzymes[24].

Because postoperative pain involves both central component and inflammatory response andbecause opioid analgesics are devoid of anti-inflammatory activities[25], it is conceivable that addition of anti-inflammatory analgesics to opioids have reduced pain intensity.

Dexamethasone has been shown to improve postoperative pain[26], although the mechanism is not understood but it may improve analgesia by virtue of its anti-inflammatory property.

Further studies are needed to explore the mechanisms by which different analgesic drugs interact to improve the duration of analgesia and pain intensity and elucidate long-term effects of this combination.

CONCLUSION

Preoperative combination of low dose morphine, paracetamol, diclofenac NA and dexamethasone together with fentanyl represents a good analgesic regimen resulting in prolonged postoperative analgesia, decreased pain intensity, and reduced rescue analgesic dosage with no notable adverse effects. As a result, this combination in the reported doses can be used routinely with general anesthesia unless contraindicated.

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