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STUDY COMPARING PREEMPTIVE ANALGESIC EFFECTS OF ORAL GABAPENTIN AND CLONIDINE AGAINST PLACEBO IN TOTAL ABDOMINAL HYSTERECTOMY UNDER COMBINED SPINAL EPIDURAL ANAESTHESIA

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ABSTRACT

Abdominal hysterectomy usually requires multimodal analgesic regimen for optimal perioperative analgesia. Through this study we aim to assess the significance of preemptive analgesia as well as to compare the efficacy of two analgesics - Clonidine and Gabapentin in abdominal hysterectomy. To compare the postoperative analgesia, sedation and side effects of oral Gabapentin, Clonidine and placebo given as preemptive analgesics in patients undergoing Total Abdominal Hysterectomy under Combined Spinal Epidural Anaesthesia Design. Randomized Controlled study **.** One hundred and twenty American Society of Anesthesiologists' Physical Status 1& 2 patients posted for elective abdominal hysterectomy were randomly allocated into three groups- group G received preemptive analgesia with T. Gabapentin 300mg, Group C –T. Clonidine 0.15mg and Group P –Placebo. Hysterectomy was performed under combined spinal epidural. Patients were assessed 24hours postoperatively for pain using numerical rating scale, sedation using Macintyre Sedation Scale and other complications. Pain managed with epidural boluses and breakthrough pain with inj. Diclofenac. Total analgesic consumption in 24hours noted**.**There is significant difference in pain scores at 12 and 24 hours; P values 0.001 and 0.049 respectively. P value is 0.003 when break through pain is compared among groups; Significant difference noted between G and C (P=0.014). There is significant difference in the number of epidural and total analgesia taken by the three groups with P value < 0.001.No statistically significant difference in sedation scores and side effects. Preemptive analgesia has a definite role in reducing analgesic requirements. 300mg of Gabapentin has better preemptive analgesic effects when compared to 0.15mg of Clonidine.

KEYWORDS: Preemptive analgesia,Gabapentin, Clonidine

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INTRODUCTION

The terminology and relevance of preemptive analgesia have been one of the major controversies in pain management. Preemptive analgesia includes analgesics administered before skin incision that prevents central sensitization resulting from incisional and inflammatory injury. Although the concept of "preemptive analgesia" has been replaced by "preventive analgesia", the former still remains an important component of the latter.[1]

Variety of drugs and regional analgesic techniques have been used for preemptive analgesia. There are lots of studies that compare the effectiveness of different agents and also to find out their optimum dosages.

In this study, we have compared two different groups of drugs- Clonidine and Gabapentin. Preemptive analgesic effects of Clonidine and Gabapentin is already proven by several studies.[2,3,4,5,6] Studies that compare Clonidine and Gabapentin also exist. [7]Nevertheless studies that compare the drug dosages used in this study is lacking .

Clonidine is a centrally acting selective partial alpha2- adrenergic agonist (220:1 alpha2 to alpha1). It produces sedation, analgesia, anxiolysis and sympatholysis. High densities of $alpha_2$ receptors are present in the pontine locus ceruleus, inhibition of which causes sedation.The result is a calm patient who can be easily aroused to full consciousness. The ability of clonidine to modify the function of potassium channels in the CNS may be the mechanism for profound decreases in anesthetic requirements produced by clonidine.

Clonidine is rapidly absorbed after oral administration and reaches peak plasma concentrations within 60 to 90 minutes. The elimination half-life of clonidine is between 9 and 12 hours, with approximately 50% metabolized in the liver, whereas the rest is excreted unchanged in urine. [8]

Gabapentin is an antiepileptic drug which is also used in the treatment of neuropathic pain. It interacts with calcium channel α2-δ ligands to inhibit calcium influx and subsequent release of excitatory neurotransmitters. The elimination half-life of gabapentin is brief – 6hrs. Gabapentin is well absorbed after oral administration, is not metabolized or bound to plasma proteins, but is excreted unchanged by the kidneys. The dose should be decreased in patients with renal dysfunction. Side effects of gabapentin are somnolence, fatigue, ataxia, vertigo, and gastrointestinal disturbances.[9]

Total abdominal hysterectomy (TAH) is routinely performed via Pfannensteil incision and causes moderate to severe surgical pain that needs multimodal analgesic regimen. In our center TAH is performed under central neuraxial blockade. This study is an attempt to optimize the perioperative analgesia for Total abdominal hysterectomy.

METHODOLOGY

This study was conducted as a Randomized Controlled Double blinded study after obtaining approval of the Institutional Research Committee and Ethical Committee. Study period was eighteen months starting from April 2012. Total sample size of 120 was selected by applying statistical formula $(Z\alpha + Z\beta)^2 \times pq \times 1.5/d2$ to a previous similar study by Sussan Soltani Mohammadi and Mirsadegh Seyedi. [7]

Inclusion criteria are patients with ASA PS 1 and 11, elective surgery, anticipated duration of surgery less than three hours and age between 30 – 60years. Exclusion criteria are all contraindications to Central Neuraxial Block as well as documented allergy to local anaesthetics.

After pre-anaesthetic check up, patients to be included in the study were advised fasting for eight hours and T. Ranitidine 150mg as well as T. Metocloperamide 10mg at six a.m. with sips of water. Patients were randomly allocated into three groups of 40 each by using computer generated randomization chart. Study groups were Group G- who received T. Gabapentin 300mg, Group C –who received T. Clonidine 0.15mg and Group P –who received Placebo. All study medications were given orally with sips of water one and a half hour prior to the planned procedure by a person who is not involved in the study.

In the operation room, monitors including five-lead ECG, pulse oximetry, Non invasive blood pressure were attached, baseline values noted and monitoring continued throughout the perioperative period. Inj. Midazolam 1mg was given intravenously before attempting central neuraxial blockade. All patients were co-loaded with 10ml/kg of Ringer Lactate. Combined spinal epidural was performed at $L_{2/3}$ or $L_{3/4}$ interspace. 3.5ml of 0.5% Bupivacaine Heavy was given in subarachnoid space. Vitals monitored and kept stable throughout the perioperative period.

After surgery patients were shifted to the Intensive Care Unit. Patients were assessed at 1, 2, and 4,8,12 and 24 hours after surgery by an independent physician who is not aware of the group allocations. Pain assessment was done using Numerical Rating Scale ranging from 0 to 10; 0 with no pain and 10 with worst imaginable pain. 12ml 0.125% bupivacaine was given epidurally for a pain score of more than 3 on Numerical Rating Scale. Sedation was assessed using Macintyre Sedation Scale.[10]

0 Awake, alerts

1 Mild sedation, easy to arouse

1S Asleep, easy to arouse

2 Moderate sedation, easy to arouse, unable to remain awake

3 Difficult to arouse

Patients and nursing staff were also enquired about any other complications. If pain recurs within four hours of epidural analgesia, rescue analgesia was given with inj. Diclofenac 50mg intramuscularly.

Total consumption of epidural analgesia, rescue analgesia and total episodes of breakthrough pain are assessed at 24 hours.

Statistical analysis

Data was analyzed using SPSS software Version 21.0. One way Analysis of variance was used to compare age and weight among different groups. Sedation scores assessed using proportions and Chi-square tests. KruskalWalli's ANOVA was carried out for comparison of pain scores in 24hrs and break through pain. One way analysis of variance was carried out for comparison of number of analgesia intake by three groups.

RESULTS

Patients in three groups were comparable with respect to age (P value--0.725) and weight (P value-0.061).

Table 1
Comparison of pain scores among three groups

Group	Pain1	Pain2	Pain4	Pain8	Pain12	Pain 24
P	1.30	2.77	2.57	2.15	3.00	1.75
G	1.55	2.83	3.20	2.10	2.25	1.08
C	.78	2.05	2.10	1.90	1.33	.98
Chi square	3.389^{ns}	2.635^{ns}	4.528^{ns}	0.178^{ns}	13.430**	6.033**
P-value	0.184	0.268	0.104	0.914	0.001	0.049

Ns non significant at 0.05 level; ** significant at 0.01 level

Table 2
Pair wise comparison of pain scores at 12th and 24th hour using Mann Whitney U test

Groups	Pain 12		Pain 24	
	Z-value	P-value	Z-value	P-value
Comparison between P and G	1.811	0.070	2.164	0.030
Comparison between P and C	3.708	< 0.001	1.994	0.046
Comparison between G and C	1.756	0.079	0.194	0.846

Table 3
Comparison of Break through pain among three groups

Group	Br pain
P	2.32
G	1.15
C	1.97
Chi square	11.703**
P-value	0.003

***** significant at 0.01 level***

For comparison of break through pain, KruskalWalli's ANOVA was carried out. There exists significant difference between three groups. Hence, Mann Whitney U test was carried out for comparing pair wisely. Significant difference was noted between G and C (Z = 2.462; P=0.014).

Table 4
Comparison of number of analgesia intake by three groups

Group	Voveran		Epidural analgesia		Total analgesia	
	Mean	SE	Mean	SE	Mean	SE
P	0.90	0.118	3.68^{a}	0.169	4.58^{a}	0.202
G	0.68	0.115	2.55^{b}	0.156	3.23^{b}	0.207
C	0.55	0.094	2.90^{b}	0.189	3.45^{b}	0.221
F-value	2.616^{ns}		11.218**		11.847**	
P-value	0.077		< 0.001		< 0.001	

Table 5
Comparison of sedation among groups

Group	Sedation score 1	Sedation score 2	Sedation score 4	Sedation score 8	Sedation score 12	Sedation score 24
Chi square	3.552	2.683	3.907	2.991	7.093	0.556
P-value	0.737	0.612	0.689	0.810	0.312	0.757

Table 6
Complications in the three groups

Complication	P		G		C	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
Bradycardia	0	0	0	0	1	2.5
Nausea	1	2.5	0	0	1	2.5
Vomiting-	0	0	1	2.5	1	2.5

DISCUSSION

This study is an attempt to compare the preemptive analgesic effects, sedation and side effect profile of Clonidine and Gabapentine against a placebo in patients undergoing total abdominal hysterectomy under combined spinal epidural anaesthesia. Total sample size is 120 distributed in three groups of 40 each. None of the cases have been dropped out. Patients in the three groups are comparable with respect to age (P value 0.725) and weight (0.061).

Comparison of pain scores carried out by KruskalWalli's ANOVA at 1,2,4,8,12 and 24 hours shows P-values of 0.184,0.268,0.104,0.914,0.001 and 0.049

respectively. That means there is a significant difference in pain scores at 12 and 24 hours. Comparison between groups G and C alone shows P value of 0.079 at 12^{th} hour and 0.846 at 24^{th} hour i.e. there is no statistically significant difference in pain scores between G and C.

The P value is 0.003 when break through pain is compared among groups, which is statistically significant. Hence, Mann Whitney U test was carried out for comparing pair wisely. Significant difference was noted between G and C (Z = 2.462; P=0.014).

In a study by Sussan Soltani Mohammadi and Mirsadegh Seyedi that compared 300mg Gabapentin with 0.2mg Clonidine, patients in Placebo and Clonidine group had statistically more pain than Gabapentin group in first 6 hours after surgery.[7] In a study by Sudar Kodi et al. to assess the effects of oral Clonidine premedication(0.1mg) on the duration of analgesia by bupivacaine subarachnoid block, the duration of post-operative analgesia in control group was 115.90 ± 12.40 min and in Clonidine group was 183.30 ± 20.21 min which is statistically highly significant.[4]

One way analysis of variance has been carried out for comparison of number of analgesia intake by three groups. F-value is found to be significant in the case of epidural and also total analgesia. This shows that there is a significant difference in the number of epidural and total analgesia taken by the three groups with P value < 0.001. LSD test has been carried out for pair wise comparison in both the cases. It is observed that number of analgesia taken is higher in the case of placebo compared to the other two groups. The Mean of total Diclofenac consumption is also higher in the placebo group though it is not statistically significant.

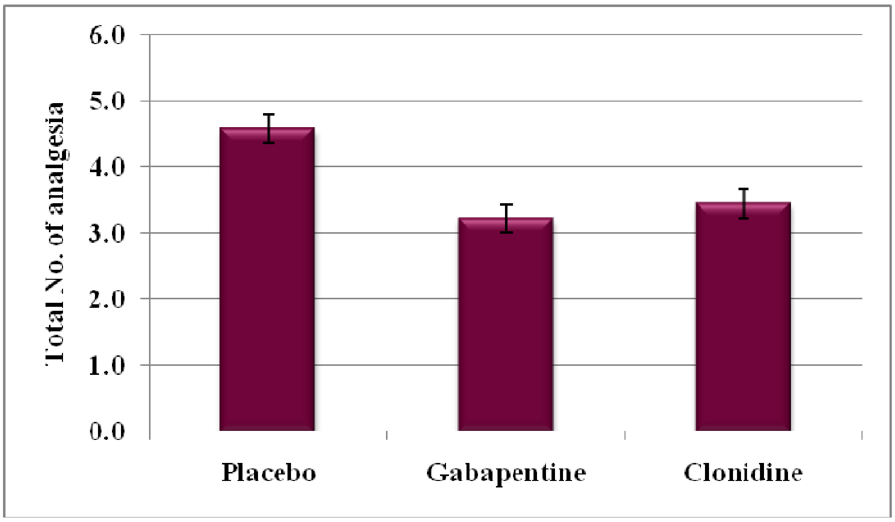

Figure 1
Comparison of total analgesic consumption in 24 hours

Mean morphine consumption was less with Gabapentin compared to Placebo and Clonidine in the study by Sussan Soltani Mohammadi and Mirsadegh Seyedi.[7] This difference was also statistically significant. (P values Clonidine vs placebo 0.032; Gabapentin vs placebo 0.024; Gabapentin vs Clonidine 0.045)

In another study comparing 300 mg Pregabalin, 900 mg Gabapentin and placebo in 90 women undergoing abdominal hysterectomy, the difference in the Diclofenac consumption was statistically significant between Pregabalin and control groups, and Gabapentin and control groups.[6]

All the above mentioned comparisons definitely point out the significance of preemptive analgesia in reducing postoperative analgesic requirements.

From this study it is also observed that 300mg of Gabapentin has better preemptive analgesic effects when compared to 0.15mg of Clonidine. This is because the incidence of breakthrough pain is more with Clonidine compared to Gabapentin which has got statistical significance also. The total analgesic consumption in 24 hours is less with Gabapentin compared to Clonidine though it is not statistically significant.

There is no statistically significant difference in sedation scores among three groups in our study. Comparison of sedation scores carried out at 1, 2, 4, 8,12and24 hours shows P-values of 0.737, 0.612, 0.689, 0.810, 0.312 and 0.757 respectively.

Side effect profile in this study is not at all statistically significant. Only one patient in Group C developed bradycardia, two patients – one each from Group P and C complained of nausea and two patients – one each from Group G and C developed vomiting. All of them responded well to routine management. The common side effects in the study by Anju Ghal et al. that compared pregabalin, gabapentin and placebo were somnolence, dizziness, nausea and vomiting. [6] Post Operative Nausea and Vomiting was not statistically different between the study groups during first 6 h after the operation (Chi-square, p>0.05) in the study by Sussan Soltani Mohammadi and Mirsadegh Seyedi.[7]

CONCLUSION

Preemptive analgesia has a definite role in reducing postoperative analgesic requirements. 300mg of Gabapentin has better preemptive analgesic effects when compared to 0.15mg of Clonidine. No significant difference in level of sedation and complications among groups.

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