The combined analgesic effect of gabapentin and transdermal fentanyl patch on acute and chronic pain after maxillary cancer surgeries

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Abstract Purpose of this study was to evaluate the combined analgesic effect of gabapentin and transdermal fentanyl patch, on acute and chronic pain after surgery for maxillary cancer.

Study design The Study was double blind and prospective. 100 subjects belonging to ASA grade I and II, 30–50 years age group, scheduled for maxillary cancer surgery were randomized into two groups; treatment group (GT): to receive gabapentin, transdermal fentanyl patch or control group ©: two placebos. For acute postoperative pain (Visual Analogue Score) and analgesic requirements were assessed 2, 4, 8 hours and 7 days after surgery. Subjects were also assessed for chronic pain 2, 4, 6 months later.

Results Subjects in treatment group required lesser dose of analgesic, as compared to control group, in the post operative period. Visual Analogue Scores were also significantly lower in the treatment group throughout the post operative period. Occurrence of side effects was non significant between both groups. 2, 4 and 6 months after surgery, 40, 35 and 28 subjects respectively, out of total 45 subjects of the control group, reported chronic pain. In comparison, 25, 10 and 4 subjects out of 42 subjects in the treatment group reported chronic pain 2, 4, 6 months respectively after surgery. 15, 10 and 6 out of 45 of the control group required analgesics, whereas 2, 0 and 0 out of 42 in the treatment group, required analgesics respectively 2, 4 and 6 months after surgery

Conclusion Acute and chronic pain after maxillary cancer surgery is significantly reduced by multimodal analgesia.

Keywords Transdermal fentanyl · Maxillary cancer · Gabapentin

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Introduction

Surgery with cervical node dissection, combined with chemotherapy or radiotherapy, is currently the treatment of choice for the maxillary malignancies. However, these surgeries are associated with scars, injury of soft tissues and of sensory afferents, which innervate the surgical area, particularly after the dissection of cervical lymph nodes. So, all these contribute to acute and chronic pain. Infact, postoperative pain may also influence the development of chronic pain.

In a retrospective cohort study of maxillectomies over a 5 year period, the

cumulative prevalence for persisting post maxillectomy pain was 45% overall but reached 60% [1]. This pain may substantially affect the quality of life of men treated for maxillary cancer. This is a major problem considering the number of men operated on for maxillary cancer.

Acute and chronic pain management after maxillary cancer surgery has been investigated previously. Regimens providing efficient postoperative analgesia and reducing analgesic consumption for acute pain relief usually do not prevent development of chronic pain [2]. But, gabapentin may have some beneficial effect in this regard [3]. There are similar reports

with use of preoperative Transdermal fentanyl (TF) patch application, to decreases acute pain scores and morphine consumption in the Post Anaesthesia Care Unit [4,5,6]. So the purpose of this study was to evaluate the combined analgesic effect of gabapentin and TF patch, on acute and chronic pain after surgery for maxillary cancer.

Methods

After getting a written informed consent from all subjects. 100 men, aged between 30–50 years, of ASA physical status I or II,

average height of 145–165 cm and $\pm 20\%$ of the ideal body weight, admitted for maxillary cancer surgery, were enrolled in the study, between March 2005–08. Inclusion criteria included the subjects, scheduled for radical neck or modified radical neck dissection surgeries and are opioid tolerant. Patients with chronic pain of any cause, consuming analgesics, antidepressants, calcium channel blockers, antiepileptic, sedatives, or hypnotics during the last month, hypersensitive to opioids, any respiratory disease and those with inoperable maxillary cancer were excluded from the study.

The study design was double blind, and prospective. All subjects were admitted 2 days before surgery. The Visual Analogue Scale (VAS) scoring pain was explained to all subjects. Subjects were also informed that some treatment will be given, that might be helpful in attenuating postoperative pain. Subjects were selected using simple randomized sampling were allocated to either of the two groups using sealed opaque envelopes, by the numbers randomly generated by computer table. An independent anesthesiologist who did not participate in the study or data collection made the group assignments.

Control group C (treated with placebo capsules, placebo transdermal patch)

Treatment group GT (treated with gabapentin, TF patch)

Placebo capsules were made identical in appearance to gabapentin capsules and similarly, placebo patches were identical to TF patch. Same number of capsules were packed in group specific bottles and coded as bottles A and B for the group C and GT respectively. After randomization, patients were treated as follows:-

Group C received placebo capsules from bottle A every 6 hours, starting the evening before surgery (6 pm) and continued until the 7th postoperative day. Patients also received a placebo patch applied to a clean, dry area on the upper arm, once in the evening (6 pm) before surgery to be removed next morning 2 hrs before surgery. Hairs were clipped from the site, prior to applying the patch. Patch was pressed firmly for 30 seconds to make sure the patch stays in place. Patient also received Ondansetron 4 mg IV BD during preoperative period before surgery.

Group GT received 400 mg Gabapentin tablets (Gabatin, Neon Labs, Mumbai) and TF patch (Duragesic, Johnson and Johnson Ltd, Mumbai) (release at 25mcg/hr) from bottle B, to be administered with the same plan as group C. Ondansetron was also administered, in similar way to group C.

Fig. 1 Diclofenac requirements

Fig. 2 Visual Analogue Score during postoperative period

All subjects fasted for 12 hours and no premedication was given. Standard monitoring with Non-Invasive Blood Pressure (NIBP), electrocardiography and pulse oximetry was done. All subjects received glycopyrrolate 0.2 mg and were pre-oxygenated for 3–4 minutes. Anaesthesia was induced with propofol 2 mg/kg body wt IV and Rocuronium 0.9mg/kg body wt IV. Lidocaine 1.5mg/kg IV was given 90 sec before laryngoscopy. Anesthesia was maintained with 1% Isoflurane, and nitrous oxide/oxygen combination (60/40). At the end of surgery, neuromuscular block was antagonized with neostigmine 0.5 mg/kg body wt and Glycopyrrolate 0.01 mg/kg body wt IV, patients were extubated, and transferred to the postoperative care unit.

All subjects remained in the postoperative care unit (POCU) for at least 2 hrs. Subjects who complained of pain in POCU received 75mg inj. Diclofenac sodium IM (Voveran inj., Biochemie Novartis India Ltd, Mumbai). In the ward, 100 mg Diclofenac sodium (Voveran, Biochemie Novartis India Ltd, Mumbai) tablets were given, if required. Acute postoperative pain was assessed by an anesthesiologist blinded to group allocation, using VAS scoring (horizontal line from 0–100, with 0 represented no pain and 100 representing maximal unbearable pain). Patients were asked to draw a point in the horizontal line denoting present intensity of their pain. Pain was assessed 2, 4, 8 hours after surgery and each morning, until 7th day after surgery.

On discharge from hospital, patients were instructed to note the pain they might have at home and the analgesic required to counter the pain. Chronic pain was defined as presence of pain 2 months after surgery, independent of its intensity or analgesic requirements. Patients were interviewed 2, 4 and 6 months after surgery by blinded anesthesiologist to find out whether they experienced pain or decreased sensation in the operated site and analgesic requirements.

With 80% power (20% beta error) and 95% confidence level (5% alpha error), assuming standard deviation of 0.4 tablet estimated from initial pilot observations, the sample size calculated was 33, in each group. Power was given at 0.8 to detect a 50% reduction in analgesic consumption between two groups for first 7 postoperative days, and also 50% reduction in chronic pain, at $P < 0.05$ (two-sided). For the purpose of our study, we have taken 50 subjects in each group.

Table 1 Patient characteristics

	Control Group	Treatment Group	t value	p value
Age (yr) (n=50)	41±8.1	40±8.2	0.6135	0.5410
Body weight (kg) (n=50)	54±6.9	55±8.0	0.6693	0.5049
Height (cm) (n=50)	153±4.1	154±4.3	1.190	0.2369

Table 2

	Control group	Treatment group	t value	p-value
Duration of surgery (min)	140±17.3	141±19.2	0.2376	0.7850
Time to first analgesia in POCU (min)	32±9.1	49±6.7	10.637	<0.0001
No. of pts requiring Inj. Diclofenac IM in POCU	32	10		0.0050
Diclofenac tablets during the first 7 postoperative days	0.98±0.58	0.24±0.27	8.204	<0.0001

Table 3

No. of patients	2 months			4 months			6 months		
	C (n=45)	GT (n=42)	p-value	C (n=45)	GT (n=42)	p-value	C (n=45)	GT (n=42)	p-value
Facial Pain	8	7	1.0000	5	4	1.0000	4	4	1.0000
Pain during mastication	20	9	0.1321	12	7	0.4501	10	4	0.2486
Chronic Pain	40	25	0.2509	35	10	0.0046	28	4	0.0003
Absent or decreased Sensation	12	10	1.0000	12	10	1.0000	12	10	1.0000
No. of patients requires analgesics	15	2	0.0063	10	0	0.0044	6	0	0.0305

Sample size was calculated using power and sample size calculator by department of Biostatistics, Vanderbilt University, USA.

Statistical calculations were made by analysis of variance test. Patient characteristics, duration of surgery, time to 1st analgesic requirements, number of Diclofenac tablets consumed by each group of patients during 1st 7 days after surgery and VAS scoring at rest were compared using paired and unpaired student t test. The Diclofenac requirement in the POCU, chronic pain in the neck and maxillary area, absent or decreased sensation and number of patients in each group who require analgesics were compared between the groups using Fisher's exact test. The SPSS 11 software was used for statistical analysis.

Results

1. Patient characteristics and duration of surgery were found to be similar among the both groups (Table 1).
2. The time to first analgesic requirement was found to be significantly ($p < 0.0001$) higher in GT group (49±6.7) as compared to C group (32±9.1) (Table 2)
3. The number of patients who required analgesia in POCU (10 in GT group and 32 in C group) and the number of diclofenac tablets required for the first 7 postoperative days (0.24±0.27 in GT group and 0.98±0.58 in C group) were found to be significantly lower in GT group as compared to C group, respectively. (Table 2, Fig. 1)

4. VAS scoring was found to be significantly lower in GT group as compared to C group, throughout the 7 postoperative days (Fig. 2).
5. Two months after surgery, the total incidence of chronic pain at any site, and the incidence of abnormal sensation did not differ among the groups. However, the number of patients that required analgesics at home to relieve postsurgical pain was significantly decreased in the GT group (Table 3)
6. The total incidence of chronic pain at any site and the number of patients that required analgesics at home to relieve postsurgical pain was significantly decreased in the GT group, 4 and 6 months after surgery (Table 3).
7. Also, incidence of arm pain was found to be significantly lower in GT group after 6 month of surgery (Table 3).
8. For the doses given and the duration of administration, both drugs were almost entirely free of adverse effects.

Discussion and Conclusion

Our results demonstrate that the drugs administered as per protocol of the study, significantly reduced the requirement of analgesics throughout the postoperative period. Also, the development of chronic pain was significantly reduced four months after surgery.

Fentanyl, a synthetic opioid agonist interacts primarily with the μ (mu) receptor. The low molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery by the transdermal therapeutic system. The use of transdermal fentanyl patch therefore is well established and accepted indication, in the treatment of chronic cancer pain, as indicated by recent review articles [7–9]. In our study, TF patch was applied once in evening, one day before surgery and that too was removed next morning, 2 hours before surgery (t 1/2 β after transdermal administration: 13 to 22h). Our aim was to achieve more consistent serum levels of fentanyl during intraoperative period and to reduce analgesic requirement during the early postoperative period.

As with other opioid agents, the most frequently observed adverse events during TF treatment is hypoventilation. It has occurred in three (2%) of the 153 patients with cancer pain during the previously premarketing trial. Clinically

relevant fentanyl-induced respiratory depression, however, was not observed during the previous three randomized trials [10–12]. In our study, for the doses given along with duration of administration of TF patch, there was no observable respiratory depression. Further, any expected incidence of nausea and vomiting was prevented by the prophylactic use of Ondansetron, as per protocol of our study.

Gabapentin has been shown to reduce analgesic requirements for acute postoperative pain. It was introduced as an antiepileptic and is extensively used in the treatment of neuropathic pain [13–15]. The drug at clinically relevant concentrations reduces the membrane voltage-gated calcium currents in dorsal root ganglia neurons of neuropathic rats and, to a lesser degree, in nonneuropathic rats [16]. It may produce analgesia by decreasing neurotransmitter release by sensory neurons, a calcium-dependent process. Mechanisms of prevention of chronic pain after injury by gabapentin are not clear. With regard to neurogenic processes, in the rat, gabapentin suppresses the ectopic discharge activity from injured peripheral nerves [17] and blocks the injury-induced neuronal hyperactivity [18]. Excitatory transmission in the spinal cord was inhibited by gabapentin only in preparations from neuropathic animals showing hyperalgesia and not from normal animals [19].

Side effects reported for gabapentin are somnolence, confusion, dizziness, and ataxia [13]. However, the drug was given for 8 weeks to doses titrated upto 3600 mg/d, unless severe adverse effects were developed. We did not observe intolerable side effects for the daily dose and the duration of treatment, as determined by the protocol of the study. Some sedation that our patients exhibited, particularly in the beginning of treatment, is desirable before and immediately after surgery. This analgesic treatment was not associated with adverse effects and may be appropriate not only for those patients who suffer, but also prophylactically to all patients who are potential candidates for developing chronic pain.

The effective treatment of acute pain usually is not associated with the prevention of chronic pain. In our study, the use of TF patch along with gabapentin proved as effective as previous analgesic regimens to prevent acute postoperative pain but superior in preventing chronic pain after maxillary cancer surgery for

cancer. Also, oral gabapentin and the application of TF patch are preferable over parenteral analgesia.

The incidences of chronic pain four and six months after surgery, was 23%, 8% in the treatment group and 77%, 62% in the control group, respectively. Our study was not powered for chronic pain assessment six months after surgery, but a larger clinical trial may show a significant difference in chronic pain between treatment and control groups at this time point.

Multimodal analgesia with TF patch and gabapentin reduced analgesic consumption after maxillectomy for cancer, without side effects. The incidence of chronic pain development, and the long-term analgesic requirements associated with maxillectomy were also less throughout postoperative period. More studies are required to investigate chronic pain for longer periods of time, as chronic pain may persist in duration and intensity beyond the six-month period.

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