Gabapentin provides effective postoperative analgesia whether administered pre-emptively or post-incision

[La gabapentine fournit une analgésie postopératoire efficace, qu'elle soit administrée avant ou après l'incision]

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Purpose: We investigated the effects of pre-incision and post-incision administration of gabapentin on postoperative pain and fentanyl consumption associated with open donor nephrectomy.

Methods: Sixty ASA I subjects were randomly allocated into three groups to receive gabapentin 600 mg two hours before surgery and placebo after surgical incision (pre-incision group), placebo two hours before surgery and gabapentin 600 mg after surgical incision (post-incision group), or placebo two hours before surgery and after surgical incision (placebo group). After surgery, pain was assessed using a visual analogue scale (VAS), (1–10 cm) at time points 0, 6, 12, 18, and 24 hr. Subjects received patient-controlled-analgesia (fentanyl 1.0 $\mu g \cdot kg^{-1}$ subject activated dose). Total fentanyl consumption in each group was recorded.

Results: Subjects of pre-incision and post-incision groups had lower VAS scores at all time points (3.1 ± 1.8, 2.9 ± 1.3, 2.8 ± 1.3, 2.5 ± 0.9, 2.5 ± 1.5 and 3.6 ± 1.1, 3.0 ± 1.2, 3.2 ± 1.1, 2.9 ± 1.0, 2.6 ± 2.2) compared to placebo group (6.6 ± 1.3, 5.0 ± 1.0, 4.4 ± 0.7, 4.2 ± 0.8, 3.9 ± 1.0). They also used less fentanyl (563.3 μg ± 252.8 and 624.0 μg ± 210.5 respectively) compared to placebo (924.7 μg ± 417.5), ($P < 0.05$). No difference in total fentanyl consumption and pain scores at any time points were observed between pre- and post-incision groups.

Conclusion: Pre-incision administration of 600 mg gabapentin has no added benefit over post-incision administration in terms of pain scores and fentanyl consumption in subjects undergoing open donor nephrectomy.

Objectif : Nous avons vérifié les effets de la gabapentine, administrée avant ou après l'incision, sur la douleur postopératoire de même que la consommation de fentanyl lors d'une néphrectomie chez un donneur vivant.

Méthode : Soixante sujets d'état physique ASA I, répartis au hasard en trois groupes, ont reçu 600 mg de gabapentine deux heures avant l'opération et un placebo après l'incision chirurgicale (groupe pré-incision), un placebo deux heures avant l'opération et 600 mg de gabapentine après l'incision (groupe post-incision) ou un placebo deux heures avant l'opération et après l'incision (groupe placebo). La douleur postopératoire a été évaluée par une échelle visuelle analogique (EVA), de 1 à 10 cm à 0, 6, 12, 18 et 24 h. Les sujets ont eu une analgésie auto-contrôlée en doses de 1,0 $\mu g \cdot kg^{-1}$. La consommation totale de fentanyl de chaque groupe a été notée.

Résultats : Les sujets des groupes pré-incision et post-incision ont présenté les scores les plus bas à l'EVA, pour toutes les mesures (3,1± 1,8; 2,9 ± 1,3; 2,8 ± 1,3; 2,5 ± 0,9; 2,5 ± 1,5 et 3,6 ± 1,1; 3,0± 1,2; 3,2 ± 1,1; 2,9 ± 1,0; 2,6 ± 2,2), comparativement au groupe placebo (6,6 ± 1,3; 5,0 ± 1,0; 4,4 ± 0,7; 4,2 ± 0,8; 3,9 ± 1,0). Ils ont aussi utilisé moins de fentanyl (563,3 μg ± 252,8 et 624,0 μg ± 210,5 respectivement) que le groupe placebo (924,7 μg ± 417,5), ($P < 0,05$). Aucune différence de consommation totale de fentanyl et de scores de douleur n'a été observée entre les groupes pré-incision et post-incision.

Conclusion : L'administration pré-incision de 600 mg de gabapentine n'a pas d'avantage sur l'administration post-incision quant aux scores de douleur et à la consommation de fentanyl chez des donneurs vivants qui subissent une néphrectomie.

GABAPENTIN is an anticonvulsant, structurally related to γ-aminobutyric acid. Experimental models of neuropathic pain and inflammatory hyperalgesia demonstrate that gabapentin has an effective antinociceptive or antihyperalgesic action, in addition to being an anticonvulsant.[1] Gabapentin has been demonstrated to act within the spinal cord or brain to reduce sensitization of dorsal horn neurons.[1] It is not effective in reducing immediate pain from injury, but it appears to reduce abnormal hypersensitivity induced by inflammatory responses or nerve injury.[1]

In the present study, we investigated the analgesic effects of pre-incision and post-incision administration of a single dose of 600 mg of gabapentin on pain and fentanyl consumption in the postoperative period (until 24 hr postoperatively) in subjects undergoing open donor nephrectomy.

Material and methods

The Institute's Ethics Committee approved this study, and written informed consent was obtained from each participant. Sixty subjects, ASA physical status I, of both sexes and scheduled for open donor nephrectomy were recruited for this double-blind, prospective, randomized and placebo-controlled study. Assuming that a 25% reduction in the mean fentanyl consumption with 30% variability among the groups would be of interest, the study required 20 subjects in each group for a power ß = 85% and α = 0.05. All healthy kidney donors undergoing open nephrectomy were included, except those who exceeded 20% of ideal body weight; were older than 60 yr or younger than 18 yr; had a history of hypersensitivity to any drug, or had a history of peptic ulcer. Excluded also were subjects who had received analgesics within 24 hr before scheduled surgery or received sedatives other than those determined by protocol, subjects on antidepressant and calcium channels blockers, or those who could not demonstrate adequate skill to use patient-controlled-analgesia (PCA) pump.

The day before surgery, all subjects were assessed and the study protocol, use of the PCA pump, and the visual analogue scale (VAS) at 1–10 cm scale (0 = no pain, 10 = worst pain imaginable) were explained. All subjects received oral lorazepam 0.04 mg·kg⁻¹ the evening before surgery and on the morning of surgery. Subjects were randomly assigned into one of three groups using a computer generated table of random numbers to receive the medications. Medication (gabapentin or matching placebo) was supplied in patient number-specific coded pouches, each containing two sachets for pre- or post incision, and were administered as follows:

Pre-incision group: received two capsules of gabapentin 300 mg each two hours before surgery, and two capsules of matching placebo through a nasogastric tube after surgical incision.

Post-incision group: received two capsules of matching placebo orally two hours before surgery and two capsules of gabapentin 300 mg each through a nasogastric tube after surgical incision.

Placebo group: received two capsules of matching placebo two hours before scheduled surgery and two capsules of placebo through a nasogastric tube after surgical incision.

The pre-incision capsules were taken by subjects orally with sips of water, whereas post-incision capsules were dissolved in 10 mL of water, and administered through the Ryle's tube. The Ryle's tube was flushed again with 10 mL of water after drug administration.

In the operating room standard monitoring was used. Anesthesia was induced with propofol 2 mg·kg⁻¹ iv and fentanyl 3 µg·kg⁻¹ iv, lidocaine 1.5 mg·kg⁻¹ iv and intubation of trachea was facilitated with vecuronium bromide 0.8 mg·kg⁻¹ iv. Anesthesia was maintained with a propofol infusion 100–200 µg·kg⁻¹·min⁻¹ and 70% nitrous oxide in oxygen, and intermittent fentanyl 1 µg·kg⁻¹·hr⁻¹ and vecuronium 100 µg·kg⁻¹as and when indicated. Upon completion of the surgery, neuromuscular blockade was reversed with atropine 0.02 mg·kg⁻¹ iv and neostigmine 0.04 mg·kg⁻¹ iv and subjects were extubated when adequate spontaneous ventilation was established, and they were transferred to post-anesthesia care unit (PACU). A senior resident, who was not the part of the anesthesia team and was blinded to the type of medications received by the subjects, recorded the pain scores after arrival in the PACU (0 hr) and subsequently at six-hour intervals until 24 hr on a VAS, (0–10 cm) at rest. Subjects received analgesia via PCA pump (fentanyl 1.0 µg·kg⁻¹ iv on each demand with lockout interval of 5 min). The side effects and the total fentanyl requirement in the first 24 hr were recorded. Respiratory depression was defined as inability to maintain oxygen saturation > 90% on spontaneous ventilation without supplemental oxygen, or a respiratory rate less than 8 min⁻¹.

After completion of the study, the data were decoded and were entered into the statistical software package SPSS 9.0 (Chicago, IL, USA). The mean and SD from pain scores for all subjects in all groups at time points of 0, 6, 12, 18 and 24 hr were calculated. Similarly, total fentanyl consumption in all the study groups was calculated. The demographic data were compared with a Chi-square test. One way ANOVA was used to analyze VAS scores of groups at different time points.

TABLE I Demographic data

Groups	Placebo (n = 20)	Pre-incision (n = 20)	Post-incision (n = 20)
Age	41.5 ± 12.3	44.0 ± 10.6	45.2 ± 10.3
Weight (kg)	56.7 ± 6.8	56.9 ± 7.5	54.7 ± 7.0
Male/Female	6/14	5/15	8/12
Duration of surgery (hr)	3.50 ± 0.8	3.40 ± 0.6	3.62 ± 0.8

TABLE II Visual analogue scale scores and fentanyl consumption 24·hr^{-1}

Groups	Placebo (n =20)	Pre-incision (n = 20)	Post-incision (n = 20)
0 hr	6.6 ± 1.3*	3.1 ± 1.8‡	3.6 ± 1.1
6 hr	5.0 ± 1.0*	2.9 ± 1.3‡	3.0 ± 1.2
12 hr	4.4 ± 0.7*	2.8 ± 1.3‡	3.2 ± 1.1
18 hr	4.2 ± 0.8*	2.5 ± 0.9‡	2.9 ± 1.0
24 hr	3.9 ± 1.0*	2.5 ± 1.5‡	2.6 ± 2.2
Fentanyl consumed (μg)	924.7 ± 417.5†	563.3 ± 252.8‡	624.0 ± 210.5**

*P value < 0.05 (placebo *vs* pre-incision and post-incisions).
†Power of study 84% (placebo *vs* pre-incision groups). **Power of study 82% (placebo *vs* post-incision groups). ‡P value > 0.05 at all time points (pre-incision *vs* post-incision groups).

TABLE III Side effects in different groups

Side effects	Placebo group (n = 20)	Pre-incision group (n = 20)	Post-incision group (n = 20)
Nausea	3	4	2
Vomiting	2	1	1
Fatigue	0	1	2
Drowsiness	1	1	2
Itching	2	1	1
Light headedness	0	1	2
Feeling at height	0	1	2
Lack of concentration	0	1	2
Headache	0	1	0
Total events	8	12	14

Side effects were comparable in all study groups (Z test).

Student-Newman-Keuls test was applied in case of statistical differences to determie the different subsets in these groups, and the 'Z test' was used to compare side effects. Total fentanyl consumed in each group (mean ± SD) in 24 hr was compared using one way ANOVA. A P value < 0.05 was considered significant.

Results

Sixty consecutive subjects, whose operations took place between July 2003 and August 2004, and who fulfilled the inclusion criteria, were enrolled in the study. All subjects completed the study.

The groups were comparable with respect to age, body weight, gender and duration of surgery (Table I). Subjects in pre-incision group had significantly lower VAS score at all time points compared to subjects in placebo group (Table II) and used less fentanyl (563.3 μg ± 252.8 *vs* 924.7 μg ± 417.5, P < 0.05). The subjects of the post-incision group also had lower VAS scores at all time points and used less fentanyl (624.0 μg ± 210.5) compared to the placebo group (924.7 ± 417.5 μg, P < 0.05 (Table II). The pain scores at corresponding time periods and mean fentanyl consumption were similar in the pre-incision and post-incision groups.

A total of 34 adverse events were observed in subjects during the study period, and the commonest side effects were nausea and vomiting (13 episodes, five in pre-incision and placebo groups and three in post-incision group). There were no differences in the frequency of side effects amongst the three groups.

In the present study, using a model of acute somatic/visceral pain, a single dose of 600 mg of gabapentin given two hours before surgical stimulus reduced the need for additional postoperative analgesic medication. Pain scores at rest were significantly lower in pre- and post-incision groups compared to the placebo group.

Discussion

Our study demonstrates the analgesic efficacy of 600 mg of gabapentin in subjects undergoing open donor nephrectomy. The subjects who received gabapentin (both the pre- and post-incision groups) had significantly lower VAS scores at all time points and consumed less fentanyl for their pain management compared to placebo. There was no difference in fentanyl consumption between pre- and post-incision groups.

It has been demonstrated that gabapentin alleviates and/or prevents acute nociceptive and inflammatory pain both in animals and in volunteers, especially

when given before surgical stimulus,[2] but an advantage of pre-incision (pre-emptive) administration of gabapentin could not be demonstrated in our study.

In animal models of nociception, gabapentin reduces hypersensitivity associated with nerve injury, inflammation, and pain after surgery.[3–5] It has been proposed that mechanical hyperalgesia surrounding the wound in postoperative subjects, and experimental heat-induced secondary hyperalgesia share a common mechanism (central neuronal sensitization) that may contribute to, and amplify postoperative pain, though the relative contribution of various pain mechanisms to postoperative pain has not been established.[3,6] Antihyperalgesic drugs (such as gabapentin) may have a role in prevention of postoperative pain, and the combination with other antinociceptive drugs may produce synergistic analgesic effects.[7] As gabapentin enhances the analgesic effects of morphine in healthy volunteers and the combination produces better analgesia in comparison with morphine alone,[8] the drug may exert a selective effect on the nociceptive process involved in central neuronal sensitization, and is the rationale for its use in the treatment of acute postoperative pain.[9] The antihyperalgesic effects of gabapentin result from an action at the α_2-Δ subunits of voltage dependent Ca^{++} channels which are up-regulated in the dorsal root ganglia and spinal cord after peripheral injury.[9,10] Gabapentin may also produce antihyperalgesia by decreasing glutaminergic transmission in the spinal cord.[11] In addition, it may inhibit central neuronal sensitization and hyperalgesia through an action at voltage dependent Ca^{++} channels resulting in a direct postsynaptic or pre-synaptic inhibition of Ca^{++} influx that decreases excitatory amino acid neurotransmission.[7]

We chose to compare the results of treatment groups (pre-incision and post-incision groups) on the basis of the findings in laboratory animals (as clinical trials are lacking) that pre-incision administration of gabapentin is substantially more effective and longer-lasting than post-incision administration.[12] It has been demonstrated that pretreatment with single dose of gabapentin blocked the development of hyperalgesia and tactile allodynia for up to two days in a rat model of postoperative pain, while giving gabapentin one hour after intervention reduced symptoms for only three hours.[13] This finding was also confirmed by the Yoon and Yaksh, who reported that intrathecal gabapentin attenuated the pain behavior when given prior to the injection of formalin into the rat hind paw, but not when given after formalin.[12,14] However, in our study we did not find a difference in postoperative pain scores or fentanyl consumption in pre- and post-incision groups. In contrast to animal studies, fentanyl was used in this study at induction of anesthesia and during intraoperative period, which might have inhibited central neuronal sensitization. Though there are studies which demonstrate the effectiveness of pretreatment with gabapentin in reducing neuronal sensitization (expressed as reduced primary mechanical allodynia) in acute inflammation, and in reducing the need for postoperative pain treatment with morphine after mastectomy,[8,15] the results of these studies are not comparable to the results of our study as they did not administer gabapentin after surgical incision.

Based upon the findings of this study, we suggest that gabapentin 600 mg is effective in reducing postoperative pain and rescue analgesic requirement in subjects undergoing open donor nephrectomy. There is no difference in terms of VAS score, rescue analgesic requirement and side effects whether gabapentin is administered two hours before, or immediately after, surgical incision in cases of open donor nephrectomy.

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