Analgesic effects of preoperative gabapentin after tongue reconstruction with the anterolateral thigh flap

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Objective To investigate gabapentin's role in head and neck cancer surgery following the demonstration of the effectiveness of gabapentin in reducing postoperative pain.

Design Non-randomised open-label trial.

Setting Prince of Wales Hospital, Hong Kong.

Main outcome measures Pain scores, analgesic usage, and the frequency of adverse effects.

Patients In patients undergoing anterolateral thigh flap reconstruction after resection of tongue carcinoma, those who had an oral dose of gabapentin before surgery were compared to those who did not.

Results Postoperative pain was reduced in the gabapentin group (1.2) compared to the control group (1.7) [P=0.05]. In the gabapentin group, mean morphine (patient-controlled analgesia) use (3.5 mg), sedation scores (1.0), and antiemetic usage (0 mg metoclopramide) were all significantly reduced in comparison to the controls with respective figures of 11.4 mg, 1.6, and 12.2 mg.

Conclusion Single preoperative doses of gabapentin led to significant reductions in postoperative pain and nausea with reduced analgesic and antiemetic usage, without additional side-effects or increases in operative complications.

New knowledge added by this study
• Preoperative gabapentin is effective in ameliorating postoperative pain in patients having head and neck surgery.
• Preoperative gabapentin is well-tolerated and there is a morphine-sparing effect.

Implications for clinical practice or policy
• Preoperative gabapentin can be safely used to reduce postoperative pain in patients having head and neck surgery.
• Such therapy may be applicable to other groups of surgical patients, for whom suitable clinical trials should be considered in order to investigate possible benefit.

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Introduction

The acute postoperative pain level in patients following surgical resection and reconstruction for head and neck cancer has received little attention in clinical studies. Optimised pain control obviously improves patient comfort and where microvascular-free flaps have been used, good analgesia is also vital to reduce the sympathetic response, reduce circulating catecholamine levels and the vasoconstrictor response that may be deleterious to flap circulation. One study looking at acute pain after head and neck tumour resection concluded that as-required pain relief is not adequate for the moderate-to-severe levels of pain to be expected, and suggested intravenous patient-controlled analgesia (PCA) for the first 3 days, to be followed by use of regular oral non-steroidal anti-inflammatory drugs (NSAIDs).[1] This practice is common in many centres including our own, however, opiate- and NSAID-based regimens have known side-effects and complications.

Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA) and its usefulness in reducing postoperative pain has been demonstrated in many different clinical scenarios,[2-7] except for head and neck cancer surgery. Based on these studies, and after

discussion with our anaesthetic and acute pain care colleagues, we began using a single preoperative oral dose of gabapentin with the aim of improving pain control and reducing nausea. Possible secondary benefits included aiding mobilisation, enhancing nutrition, and improving patient satisfaction.

Methods

This study was conducted between January 2007 and October 2008 and took the form of a non-randomised open-label trial. Fifty consecutive patients with tongue cancer treated by surgical resection, neck dissection, and reconstructed with anterolateral thigh (ALT) flaps whose donor sites could be closed primarily were included in this study. Tongue reconstruction was performed by a single surgeon. The patients formed two consecutive equal-sized cohorts; the first 25 were treated in the standard manner (control group), whilst the second 25 patients were administered 1200 mg of gabapentin (generic gabapentin) [gabapentin group] preoperatively but their treatment remained the same in all other respects. Thus, this constituted a retrospective cohort study and our Institutional Review Board did not require written consent.

All patients with American Society of Anesthesiologists (ASA) status I to II were included; exclusion criteria were known allergies or other contra-indications to gabapentin as well as any of the drugs normally used for postoperative analgesia, though none were actually excluded on this basis. Patients having skin grafts for thigh donor site closure were also excluded from this study; six being excluded on this basis. One other patient with a salvage flap that failed was also excluded.

All the operations were performed with standard premedication, analgesia, and postoperative pain protocols. Patients were nursed in the head and neck surgery wards and flap perfusion monitored clinically (warmth, colour, and capillary refill). Pain was assessed using a visual analogue scale (VAS) score where 0 cm was 'no pain' and 10 cm was the 'worst pain imaginable', and noted at 3, 6, 9, and 24 hours after surgery. In addition, patients were asked which site (tongue, neck, or thigh) had the greatest pain. Side-effects of medications such as nausea, vomiting, sedation etc were specifically checked for and recorded. Descriptive statistics and Mann-Whitney U tests were used to analyse the findings.

Results

The results are summarised in the Table. The two groups were comparable with respect to mean age (controls, 64 years; gabapentin recipients, 61 years) as well as gender, weight, ASA, duration of surgery, size of ALT flaps harvested, and extent of neck dissection.

加巴噴丁對前外則股皮瓣用於舌頭重建術的鎮痛作用

目的 確定術前施以加巴噴丁（gabapentin）對於病人術後有鎮痛作用後，探討加巴噴丁在頭頸腫瘤術的角色。

設計 非隨機開放性試驗。

安排 香港威爾斯親王醫院。

主要結果測量 疼痛指數、鎮痛藥的用法、副作用的頻率。

患者 舌腫瘤切割術後進行前外則股皮瓣用於舌頭重建術的病人中，把分別有口服加巴噴丁的實驗組和沒有口服加巴噴丁的對照組作一比較。

結果 實驗組和對照組的術後疼痛指數分別為1.2及1.7（P=0.05）。受病人控制的嗎啡平均使用量、鎮痛評分及止吐藥（胃復安）的使用方面，實驗組依次為3.5 mg、1.0分及0 mg，對照組則為11.4 mg、1.6分及12.2 mg。

結論 術前單服加巴噴丁可明顯減低病人術後的疼痛指數及嘔吐次數，從而減少病人使用鎮痛藥和止吐藥的劑量，亦無增加副作用的風險及術中併發。

The mean VAS scores over the first 24 hours were significantly lower in the gabapentin group (1.2) compared to the control group (1.7) [P=0.05]. The site of greatest pain was the donor site in 23/25 (controls), 20/25 (gabapentin recipients) [P=0.1]; in other respects pain perception was vague and it was sometimes difficult for patients to differentiate between intraoral pain, neck swelling, and tracheostomy-related discomfort.

The mean morphine PCA use in the first 24 hours was 11.4 mg in the controls and was much reduced to 3.5 mg in gabapentin recipients (P=0.001). The most common early postoperative side-effect was nausea and vomiting; seven (28%) patients received a mean of 12.2 mg of metoclopramide for postoperative nausea among the controls, whilst none did so in the gabapentin group.

TABLE. Comparison of control and gabapentin patient groups

Characteristic*	Control group	Gabapentin group
No. of patients	25	25
Female:male	10:15	8:17
Mean (range) age (years)	64 (30-89)	61 (29-88)
Mean VAS score in the first 24 hours	1.7 (1.4-1.9)†	1.2 (1.0-1.4)†
Mean sedation score in the first 24 hours	1.6 (1.4-1.8)†	1.0 (0.8-1.2)†
Mean morphine PCA used in 24 hours (mg)	11.4 (9.0-13.8)†	3.5 (2.6-4.4)†
Mean antiemetic (metoclopramide) dosage used in 24 hours (mg)	12.2 (9.8-14.6)†	0

* VAS denotes visual analogue scale, and PCA patient-controlled analgesia
† 95% confidence intervals are shown in brackets

The mean sedation score in the control group was 1.6 compared to 1.0 in the gabapentin group (P=0.043). There was one case of early postoperative delirium in the controls (in the recovery area) that settled after minor sedation; that patient later admitted a history of significant alcohol intake.

There was one flap failure among the controls, which was discovered on the second postoperative day and attributed to an arterial inflow problem; the second flap used was not included in the study due to various complicating factors. The overall flap failure rate was 1 (2%) in 50. There were no major donor site problems as defined by problems for which additional treatment or hospital stay was deemed necessary.

There was no significant difference in the mean length of hospital stay in the control and gabapentin groups, the respective durations being 11 versus 10 days (P=0.1).

Discussion

A single preoperative dose of gabapentin significantly reduced postoperative pain and analgesic usage in patients who had excision of tongue cancer, neck node dissection, and tongue reconstruction with an ALT flap, without any increase in significant side-effects. In fact, the sedation score for the gabapentin group was lower, in that they were more alert compared to the controls. This may have been due to opioid-sparing following gabapentin, and/or an absence of adverse effects related to gabapentin. Previous studies often reported on patients within a limited age (18 to 65 or 70 years), whereas our results indicate its safety in even older patients, 13 (26%) of whom were aged 70 years or more.

Opiates are the mainstay of postoperative pain control, whilst nausea and vomiting are their most common side-effects. The NSAIDs are commonly used analgesics for minor surgery and adjuvants (to reduce pain and morphine requirements) in major surgery; their use is well established but may be limited in subjects with renal, gastrointestinal, and clotting disorders. Gabapentin was introduced as an antiepileptic (approved by US Food and Drug Administration [FDA] in 1993 as an adjunct drug for epilepsy). It has also been used for neuropathic pain, having gained FDA approval for treating post-herpetic neuralgia since 2002. In the UK, it is currently licensed for use in all types of neuropathic pain.

Despite the similarity in structure, gabapentin does not act via the GABA mechanism[8] or receptors, nor does it act through opioid receptors. Rather, it appears to bind to alpha-2-delta subunits of voltage-gated calcium channels,[9] which are located presynaptically and reduce the release of excitatory neurotransmitters including glutamate, noradrenaline, and substance P.[10-12]

Postoperative pain is not necessarily purely nociceptive, but may also involve complex inflammatory, neurogenic, and visceral components. The analgesic effect of gabapentin may be partly related to synergism with morphine.[13] Some studies show that it does not seem to have significant analgesic effects on its own after a single dose of 600 mg given to volunteers but does enhance the effects of morphine.[14] Gabapentin reduces hypersensitivity associated with pain after surgery in animal models,[9] and reduces incisional pain and block development of hyperalgesia and allodynia in rats.[15]

During the past few years, the efficacy of gabapentin in postoperative analgesia has been demonstrated in high-quality studies in various clinical situations. Single doses given preoperatively decreased postoperative pain, reduced analgesic consumption, and reduced pain in patients after mastectomy,[2] laparoscopic cholecystectomy,[3,4] arthroscopic cruciate ligament repair,[5] vaginal hysterectomy[6] and total abdominal hysterectomy.[7] These findings have been amply endorsed in recent systematic reviews.[16-18]

Gabapentin is well-tolerated and meta-analyses have not demonstrated significant side-effects.[17] In fact, there is a reduction of postoperative nausea and vomiting to 2%.[19,20] Though the mechanism of this effect is not clear, it may be due to indirect opioid sparing or to a direct effect on tachykinin activity.[21] Similarly its mechanism whereby it reduces postoperative delirium is unknown and may also be related to opioid sparing,[22] and with somnolence the common side-effect (in about 15% of patients).[23] In our study, there was no evidence of gabapentin-related postoperative sedation; one instance of transient delirium in the recovery room was most probably not related to gabapentin. Other reported beneficial effects include decreased preoperative anxiety.[5]

Dizziness occurs in 11 to 24%,[23,24] and supposedly limits its use in ambulatory patients. Others have reported confusion, headache and ataxia,[23,25] but the side-effect profile is otherwise favourable.

The optimal timing for administration has not been definitively established, though meta-analyses showed effectiveness if given up to 4 hours preoperatively; the drug's half-life is approximately 5 to 7 hours with pronounced clinical effects lasting up to 20 to 24 hours.[16] Some studies recommend giving the gabapentin 2 hours[3] or 2.5 hours[5] before surgery but most suggest 1 hour.

Dose response curves for analgesia are not available, so the optimal dosage is not known definitively. Some studies have suggested that single 300-mg and 400-mg doses did not attenuate acute postoperative pain after laparoscopic cholecystectomy[26] and breast cancer surgery,[27]

respectively; whilst others reported that 300 mg was effective and that 600 mg should be the ceiling dose.[28] Most recent publications, however, mostly entail single 1200-mg doses given 1 to 2 hours before surgery[2,5] whilst others have given divided doses (400 mg every 6 hours).

Good-quality studies on the control of postoperative head and neck surgery pain are lacking. These patients have major surgery involving several sites and many also have a tracheostomy, which may impair communication. Anecdotally, it is often said that neck dissection patients generally have relatively little pain due to the transection of cutaneous nerves. One of the few studies that explored postoperative pain after head and neck surgery[1] involved patients with surgery to the anterior skull base, maxillectomy, as well as major and minor neck procedures. There have been several studies examining anterolateral donor site morbidity that concentrated on long-term effects and did not specifically mention acute postoperative pain.[29-32]

The limitations of this study include its retrospective nature, the lack of randomisation and blinding (including administration of a placebo) which will be considered during further studies in which it is planned to include flap patients who require skin grafting of thigh donor sites. It is possible that in offering and gaining consent for a preoperative oral analgesic can introduce bias, however small that may be. Another limitation is that no confounding was adjusted in the controls. In addition, effects on patient nutrition, mobilisation, and satisfaction should also be assessed.

In conclusion, gabapentin may have a significant postoperative analgesic and morphine-sparing effect when given preoperatively. It is relatively expensive however, and its cost-effectiveness has not been adequately addressed. In addition, its optimal dosage has not been established. Both these issues deserve consideration.

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