



A prospective randomized crossover study of the preemptive analgesic effect of nitrous oxide in oral surgery

K. S. Ong, DDS, MS,^a R. A. Seymour, DDS, PhD,^b and J. M. L. Tan, MD, MS,^c Singapore, and Newcastle upon Tyne, UK

NATIONAL UNIVERSITY OF SINGAPORE AND UNIVERSITY OF NEWCASTLE UPON TYNE

Objective. Preliminary animal data has shown that nitrous oxide has a preemptive analgesic effect on postoperative pain. Whether a similar effect occurs in humans is not established. In this prospective randomized crossover study, we investigated the effect of preincisional versus postincisional nitrous oxide on postoperative oral surgical pain.

Study design. The trial was a crossover study where 36 patients had each of their symmetrical impacted mandibular third molars randomly scheduled for removal in 2 sessions. Each of the 36 patients acted as his or her own control; one side of the jaw was allocated randomly to receive nitrous oxide preoperatively (pretreated side) and the other side postoperatively (posttreated side). The pretreated side received 50% nitrous oxide preoperatively for 20 minutes and 100% oxygen postoperatively for 20 minutes as placebo. The posttreated side received 100% oxygen preoperatively for 20 minutes and 50% nitrous oxide postoperatively for 20 minutes. The difference in postoperative pain between the pretreated and posttreated sides was assessed by 4 primary end-points: pain intensity as measured by a 100-mm visual analog scale (VAS) hourly for 8 hours, time to first analgesic, total analgesic consumption during the first 48 hours, and a 5-point categorical patient global assessment scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent).

Results. The VAS scores did not differ between the 2 sides at any time ($P = .50$): neither did the time to first analgesic ($P = .8$), amount of total analgesic consumption ($P = .77$), and patient's global assessment differ ($P = .63$).

Conclusion. Our results do not support the preliminary animal data that nitrous oxide has a preemptive analgesic effect for postoperative pain. 50% nitrous oxide administered preoperatively for 20 minutes has no preemptive analgesic effect on postextraction pain.

(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;98:637-42)

Preemptive analgesia has been used to describe the phenomenon that an analgesic given before noxious stimulus has effects that long outlast the presence of the analgesic in the body.¹ It is the idea that pain perceived after tissue injury may be modified or preempted, by an analgesic administered before the precipitating noxious stimulus. Preemptive analgesia could decrease the sensitization of the central nervous system that would or-

dinarly amplify subsequent nociceptive input. The subsequent postoperative pain reduction and lower analgesic requirements were inferred to be a result of this preemptive analgesic effect.

Subsequent to a number of successful animal trials,² the concept of preemptive analgesia has been the focus of extensive clinical research over the past decade. The first definition of preemptive analgesia by Wall (1988)³ simply states that giving analgesic interventions before surgery may have the potential of reducing postoperative pain. As there were hardly any clinical preemptive analgesic studies during that time, Wall's concept of preemptive analgesia was based more on opinion than on evidence. In addition, he did not include the imperative to compare a preoperative intervention with postoperative intervention. This requirement was adopted shortly thereafter, as defined by an editorial by McQuay.⁴ McQuay suggested that, to most convincingly show

^aLecturer, Department of Oral & Maxillofacial Surgery, Faculty of Dentistry, National University of Singapore.

^bProfessor, Department of Restorative Dentistry, School of Dental Studies, University of Newcastle upon Tyne.

^cConsultant, Anesthesiologist, National University Hospital, Singapore.

Received for publication Oct 20, 2003; returned for revision Jan 14, 2004; accepted for publication Feb 27, 2004.

1079-2104/\$ - see front matter

© 2004 Elsevier Inc. All rights reserved.

doi:10.1016/j.tripleo.2004.02.078

preemptive analgesia, we have to compare the same intervention made preemptively and that made at a later stage by the same route. His suggestion was based on evidence from the animal studies, which have shown consistent positive preemptive analgesic effect. His model was subsequently widely used in many clinical trials to test preemptive analgesia for all types of analgesic interventions.⁵ This model was adopted in the present study.

Nitrous oxide is widely used as an anesthetic gas and as an inhalational sedation agent for day-stay minor surgical procedures in the various medical disciplines. It is said to have a good analgesic properties, and the analgesic effect of 30% nitrous oxide has been shown to be comparable with 10 mg of intramuscular morphine.⁶ Preliminary animal data has shown that nitrous oxide has a preemptive analgesic effect.⁷ Goto et al⁷ showed that 30% and 75% of nitrous oxide administered before nociceptive barrage produced a preemptive analgesic effect in a rat formalin test. The present study attempts to reproduce the results of that animal study in humans, using 20 minutes of nitrous oxide administered before or after the oral surgery.

The aim of the present study was to investigate whether preoperative nitrous oxide has a preemptive analgesic effect on postoperative pain in patients undergoing bilateral identical impacted mandibular third molar surgery under local anesthesia.

MATERIALS AND METHODS

The protocol of the study was approved by the ethics committee of the local institution and informed consent was obtained from all participating patients. Using the principal variable, the visual analog scores (VAS) for postoperative pain, and considering a difference of 10 mm as clinically significant, the sample size was calculated. Considering a type I alpha error of .05 and a type II beta error of .1, and considering that postoperative pain would be at least 50% less intense in the preemptive case than in the control, the sample size was calculated as 30 patients who required bilateral third molar surgery. This sample size matches a previous study, which studied the preemptive effect of a local anesthetic agent in third molar surgery.⁸

All cases included in this study had 2 identical impacted mandibular third molars based on orthopantomogram evidence and were aged 16 years old and above. All patients were of ASA I status. Patients were excluded if they were on analgesics or sedatives within 1 month before the trial. The study was of crossover design where patients acted as their own controls. The left and right identical impacted mandibular third molars were randomly removed at 2 different

occasions by the same surgeon. A washout period of at least 1 month was allowed between procedures.

Restricted randomization was used to decide which side of the impacted third molar in the patient's mouth would be pretreated or posttreated with nitrous oxide in the crossover design. The patient would receive either preoperative nitrous oxide or placebo (oxygen) for one surgery and then postoperative nitrous oxide or placebo (oxygen) for the other surgery. Allocation of treatments was done by the sealed envelope technique. Envelopes with cards detailing which treatment to start first were allocated to the patients on the day of surgery. An independent investigator, who would be administering the nitrous oxide opened the envelope and gave either nitrous oxide preoperatively or postoperatively according to the randomized cards. The patients were informed that 2 medical gases would be given and that the gases may or may not cause drowsiness.

For the pretreated side, 50% nitrous oxide (50:50 nitrous oxide:oxygen) was given to the patient through a nasal hood for 15 minutes. Then local anesthetic (2% lidocaine with epinephrine 1:100,000) was injected to the operative site and the nitrous oxide was maintained for 5 more minutes. After a total of 20 minutes of nitrous oxide, 100% oxygen was given and maintained for another 5 minutes through the same nasal hood to prevent diffusion hypoxia. The nasal hood was then removed and the surgical extraction completed. After the surgery, 100% oxygen was given to the patient through the same nasal hood for 20 minutes as placebo.

For the posttreated side, the patient received 100% oxygen as placebo preoperatively for 20 minutes. Surgery was carried out in an identical manner as in the pretreated side. After the surgery, the patient was posttreated with 50% nitrous oxide for 20 minutes through the same nasal hood with additional 5 minutes of 100% oxygen at the end to prevent diffusion hypoxia.

Pulse rate and the percentage of oxygenated hemoglobin (S_pO_2) of arterial blood were continuously monitored using a pulse oximeter. Patients were kept in the clinic for close monitoring of the pain experiences for the first 4 hours.

Postoperative pain experience was assessed on the basis of 4 key endpoints, which the patient was required to record in the pain diary:

Pain intensity. Patients were asked to record on a 100-mm plain visual analog scale (VAS), the intensity of pain every hour for 8 hours after the surgery. Serial VAS recorded over the 8-hour investigation periods were compiled into a graph of pain (mm) versus time (hr). The area under the graph (AUC) was measured using the trapezoidal method and recorded as AUC_{0-8} . Such a measure gives an overall assessment of each patient's pain experience throughout the investigation time periods.⁹

Table I. Demographic details of patients. Where appropriate, results are expressed as mean ± SD

Variable	
Number of subjects	36
Number of dropouts	6
Gender (male:female)	14:16
Age (yrs)	27.8 ± 4.4
Weight (kg)	65.2 ± 10.8

Time to first analgesic. Time to first analgesic is defined as the time from the end of surgery until intake of first analgesic became necessary for the patient. The patients were given 400 mg of ibuprofen when their pain was at least 30 mm on the VAS scale or when they complained that pain was moderately severe and requested analgesic.

Total analgesic consumption. As most patients with postsurgical pain have the most discomfort within 24-48 hours, total amount of analgesic (ibuprofen) consumed during the first 48 hours was recorded.

Global assessment. Patients were asked to provide an overall evaluation of the pain experience on a 5 point categorical scale, at the end of the trial. The categories of scale were 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent. Excellent = minimum pain; poor = lots of pain.

Statistical methods

All statistical analysis was done with the NCSS 2001 (NCSS, Kaysville, Utah) statistical analysis system for Windows statistical package. Data were presented as the mean with their standard deviations, and 95% confidence intervals for the mean where applicable. Demographic data, duration of operation, and amount of local anesthetic used were evaluated with paired Student's *t* test. The difference in pain scores between the 2 extractions was analyzed using the Wilcoxon matched pairs signed rank test. The comparison of time to taking of first analgesic was based upon log rank test. The total postoperative analgesic consumption was analyzed using the Mann-Whitney U test to determine if there was a significant difference between the pretreated and posttreated extractions. The global assessment was assessed by chi-squared statistic. All tests were 2 sided, and level of significance was set at .05.

RESULTS

Of the 36 patients entered into the study, 6 were excluded from the analysis: 4 patients came for the first surgery and failed to come for the second surgery, and 2 patients failed to complete the pain diary form. Thus data was obtained from 30 patients. Due to the within-subject

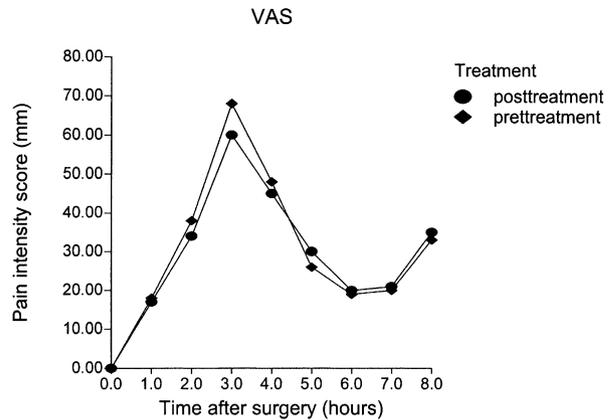


Fig 1. Mean pain intensity score (in mm) as recorded on a 100-mm plain VAS throughout the 8-hr investigation period for pretreated sides and the posttreated sides.

crossover experimental design, the influence of gender, weight, and other demographic factors, had little effect on the treatment outcomes. Demographic details of patients and operation parameter are shown in Table I. Both extractions were balanced for the operating time and amount of local anesthetic used for the surgery.

The mean pain intensity scores and AUC for VAS throughout the first 8-hour investigation period are shown in Table II and Fig 1. There was no significant difference in pain intensity as assessed by the VAS between the pretreated and posttreated sides (30.0 ± 19.8 versus 29.1 ± 17.3, *P* = .50). The time to first analgesic (2.5 ± 0.5 hr versus 2.4 ± 0.5 hr, *P* = .80), postoperative analgesic consumption (1386 ± 512 mg versus 1440 ± 465 mg, *P* = .77) and patient's overall global assessment (2.4 ± 0.9 versus 2.3 ± 0.8, *P* = .63) between the 2 sides were also similar (Table II). Fig 2 shows the patient's global assessment to the therapy at the end of the trial.

There were no cases of nausea and vomiting and no significant abnormalities in pulse rates and S_pO₂ readings in all patients owing to the administration of nitrous oxide either preoperatively and postoperatively in this study.

DISCUSSION

A recent animal study by Goto et al⁷ has shown that nitrous oxide produces a dose-dependent preemptive analgesic effect in rats. This study used the rat formalin test, where formalin is injected subcutaneously into the hind paw of the rat. This noxious stimulus evokes a progressive biphasic pain-related behavioral response that includes flinching and licking of the injected paw.^{10,11} The early phase behaviors (phase 1) begin immediately after the injection and last only 5 minutes; the more prolonged late-phase responses (phase 2) begin

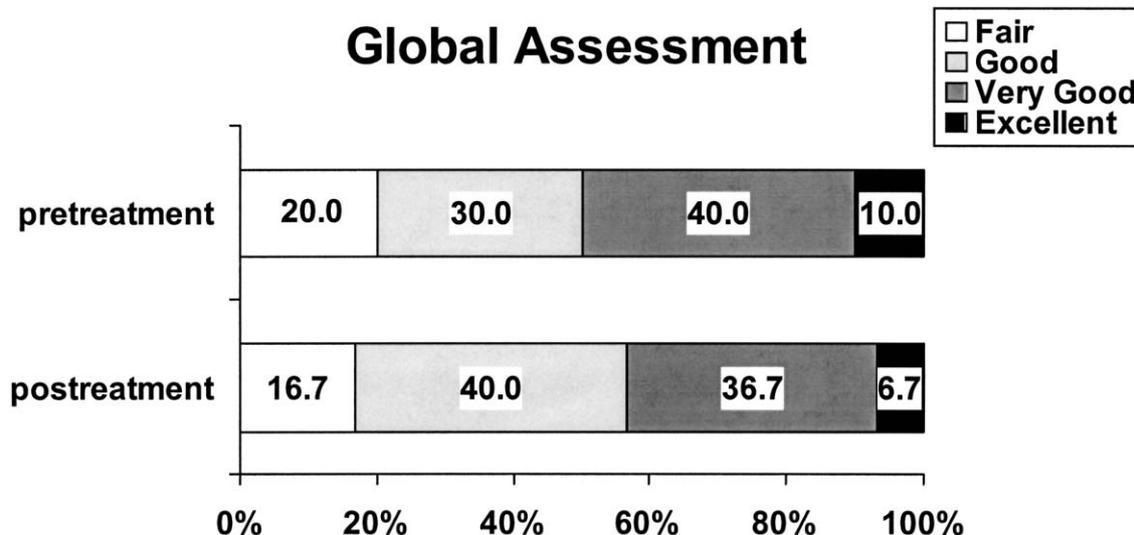


Fig 2. Patient's overall global assessment at the end of trial.

Table II. Efficacy parameters recorded in the investigation. Results are expressed as a mean ± SD, and 95% confidence intervals for the mean are shown in brackets where applicable

Variable	Pretreated side	Posttreated side	P-value
Amount of local anesthetic used (mL)	5.5 ± 0.9 (5.1-5.8)	5.6 ± 1.0 (5.2-5.9)	0.38
Mean operating time (minutes)	17.5 ± 3.7 (16.1-18.9)	18.1 ± 3.6 (16.7-19.4)	0.37
VAS (mm)	30.0 ± 19.8 (14.8-45.2)	29.1 ± 17.3 (15.8-42.4)	0.50
AUC ₀₋₈ (mm/hr)	253.5	244.5	0.50
Time to first analgesic (hr)	2.5 ± 0.5 (2.3-2.7)	2.4 ± 0.5 (2.2-2.6)	0.80
Total analgesic consumption (mg of ibuprofen)	1386 ± 512 (1196-1578)	1440 ± 465 (1266-1614)	0.77
Global assessment scores	2.4 ± 0.9 (2.1-2.7)	2.3 ± 0.8 (2.0-2.6)	0.63

There was no significant difference ($P > .05$) between the two sides in pain scores, time to first analgesic, total analgesic consumption, and global assessment throughout the study period.

about 15 minutes after injection and last 60-90 minutes. In Goto et al's study, the tail-flick test of the rat was performed as a measure of formalin-induced pain. It was shown that 20 minutes of 30% or 75% nitrous oxide administered before the noxious stimulation (formalin injection), produced a lasting effect (including the early and late-phase response) on the pain behavior in the animal. However, when nitrous oxide was given 30 minutes after the formalin injection, there was no effect on the late-phase response. There are also other formalin animal studies using opioids and local anesthetic which provided evidence that interventions made before the formalin injection produces greater inhibition of pain behavioral response than that made after formalin injection.¹²⁻¹⁴

Our present study was also done with 20 minutes duration of induction of anesthesia. Conscious sedation and not general anesthesia was planned for our study and hence only 50% nitrous oxide was used instead of 75% or higher concentration of nitrous oxide. However, our results contradict those of Goto et al. Due to a lack in

human studies of dose-response effect of nitrous oxide, it may be argued that a higher concentration of nitrous oxide for a longer period of time may lead to different results. In a recent review in preemptive analgesia by Kissin (2000),¹⁵ it was stated that the preemptive analgesic block would need to be of sufficient strength and duration to be effective. Perhaps a higher concentration of nitrous oxide for a longer duration of time, particularly when extended intra- and postoperatively, may produce a greater effect. A recent study by Gorden et al¹⁶ demonstrated that blockade of postoperative pain during the first 4 hours with bupivacaine following oral surgery resulted in less postoperative pain 1 to 2 days after surgery. This is probably true, as most of the peripheral and central sensitization occurs during the first few hours after surgery when the inflammatory mediators peak. However, such a long blockade is only possible with a long-acting local anesthetic and is clinically not feasible for nitrous oxide to be administered for 4 hours after the surgery. But it should be noted that Gordon's study compared different analgesic interventions, i.e.,

comparing preoperative lidocaine with postoperative bupivacaine and with placebo saline. It may be argued that the differences in pain experience in Gordon's study may be due to the differences in efficacy of the individual local anesthetic agents rather than the timing of interventions. To prove convincingly that bupivacaine has a preemptive analgesic effect for Gordon's study, bupivacaine needs to be administered before the surgery in one group and after surgery in another group.

There have been studies in animals and humans showing that local anesthetic could prevent central sensitization and provide preemptive analgesia.¹⁷⁻²⁰ Because the effect of local anesthetic lasts considerably longer and is probably of greater intensity than that provided by nitrous oxide, it is possible that the local anesthetic effect may have overshadowed any preemptive effect that may have been provided by nitrous oxide in this study. A less potent and shorter duration local anesthetic, e.g., 1% lidocaine without any epinephrine, than the one used in this study might provide a different result. However, a pilot study showed that 1% lidocaine without any epinephrine resulted in poor anesthesia for oral surgery.²¹ It would be a very painful experience for the patients and unethical to perform the surgery without an effective local anesthetic, as 50% nitrous oxide alone would not provide sufficient anesthesia for the surgery to be carried out comfortably.

There are probably as many negative as positive human clinical studies of preemptive analgesia.⁵ However, a recent systematic review of preemptive analgesic effect for postoperative pain by Moiniche et al²² concluded that there is little experimental support for a preemptive analgesic effect in the clinical setting.²² They reviewed 80 randomized controlled trials that compared various analgesic techniques applied before incision and later in the perioperative period. Only modest differences were noted, and these were present only with epidural injections. The reason that a robust experimental finding in the animal studies cannot be confirmed in human patients is not forthcoming, but several explanations can be considered. As explained above and in Kissin's review,¹⁵ many of the preemptive studies may not have provided an analgesic intervention that is of sufficient strength and duration for it to be effective.

Although there have been many recent animal studies that showed a positive preemptive analgesic effect,^{5,23} extrapolation of these results to humans requires caution. The animal model used may not be compatible with the human operative procedure, in which the nociceptive input is quantitatively different and present for a longer period. Formalin pain is due primarily to peripheral tissue inflammation, whereas surgical pain has both inflammatory and neuropathic components.¹⁰ Species

differences may also exist. The rat whose paw has been injected with a small volume of formalin typically shows a biphasic behavioral response composed of flinching, lifting, and licking the affected paw.¹⁰ However, these unique biphasic effect seen in rats are not present in humans. Humans have a monophasic behavioral response to formalin injection.²⁴

Future study in this area may consider extending the nitrous oxide administration into the intra- and postoperative period and compare it with placebo. In theory, this may be the more relevant time period for blocking the development of central sensitization. However, this model creates technical problems, as it may be more difficult to compare exactly similar analgesic interventions. For example, in the preemptive side for this study, the nitrous oxide would have to be administered for 20 minutes preoperatively followed by the whole duration of the surgery and beyond. It is then difficult to decide when and how much of nitrous oxide to give for the control side to be comparable with the preemptive side. The timing and total dosage are likely to be different.

CONCLUSION

This study shows that 50% nitrous oxide administered preoperatively for 20 minutes does not have any preemptive analgesic effect in humans having impacted third molar teeth extracted under local anesthesia. It may be a good adjunct for intraoperative pain control but has no effect on postoperative pain reduction when administered preoperatively.

REFERENCES

1. Dahl JB, Kehlet H. The value of preemptive analgesia in the treatment of postoperative pain. *Br J Anaesth* 1993;70:434-9.
2. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg* 1993;77:362-79.
3. Wall PD. The prevention of postoperative pain. *Pain* 1988;33:289-90.
4. McQuay HJ. Preemptive analgesia. *Br J Anaesth* 1992;69:1-3.
5. Ong KS, Seymour RA. An evidence-based medicine approach to preemptive analgesia. *Am J Pain Manage* 2003;13:158-72.
6. Parbrook GD, Rees GA, Roberston GS. Relief of postoperative pain: comparison of 25% nitrous oxide and oxygen mixture with morphine. *BMJ* 1964;2:480-2.
7. Goto T, Marota JJ, Crosby G. Nitrous oxide induces preemptive analgesia in rat that is antagonized by halothane. *Anesthesiology* 1994;80:409-16.
8. Campbell WI, Kendrick. Preemptive analgesia using local anaesthesia: a study in bilaterally symmetrical oral surgery. *Br J Anaesth* 1997;79:657-9.
9. Matthews JNS, Altman DG, Campbell MJ. Analysis of serial measurements in medical research. *BMJ* 1990;300:230-5.
10. Tjolsen A, Berge O, Hunskaar S, Rosland HJ. The formalin test: an evaluation of the method. *Pain* 1992;51:5-17.
11. Wheeler-Aceto H, Cowan A. Standardization of the rat paw formalin test for evaluation of analgesics. *Psychopharmacology* 1991;104:35-44.
12. Dickenson AH, Sullivan AF. Electrophysiological studies on the effect of intrathecal morphine on nociceptive neurons in the rat dorsal horns. *Pain* 1986;42:211-22.

13. Dickenson AH. Recent advances in the physiology and pharmacology of pain: plasticity and its implications for clinical analgesia. *J Psychopharmacol* 1991;5:342-51.
- 14.Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Res* 1990;535:155-8.
15. Kissin I. Preemptive analgesia. *Anesthesiology* 2000;93:1138-43.
16. Gordon SM, Brahim JS, Dubner R, McCullagh LM, Sang C, Dionne RA. Attenuation of pain in a randomized trial by suppression of peripheral nociceptive activity in the immediate postoperative period. *Anesth Analg* 2002;95:1351-7.
17. Taylor BK, Peterson MA, Masbaum AI. Persistent cardiovascular and behavioural nociceptive responses to subcutaneous formalin require peripheral nerve input. *J Neurosci* 1995;15:7575-84.
18. Kissin I, Lee SS, Bradley EL. Effect of prolonged nerve block on inflammatory hyperalgesia in rats: Prevention of late hyperalgesia. *Anesthesiology* 1998;88:224-32.
19. Tverskoy M, Cozakov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesth Analg* 1990;70:29-35.
20. Gottschalk A, Smith DS, Jobes DR, et al. Preemptive epidural analgesia and recovery from radical prostatectomy: a randomized controlled trial. *JAMA* 1998;279:1076-82.
21. Ong KS, Ho VCL. Pain reduction by low level laser therapy: a randomized controlled study in bilateral oral surgery. *Am J Pain Manage* 2001;11:12-6.
22. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief. *Anesthesiology* 2002;96:725-41.
23. Aida S, Baba H, Yamakura T, Taga K, Fukuda S, Shimoji K. The effectiveness of preemptive analgesia varies according to the type of surgery: a randomized, double blind study. *Anesth Analg* 1999;89:711-6.
24. Nagasaka H, Nakamura S, Mizumoto Y, Sato I. Effects of ketamine on formalin-induced activity in the spinal dorsal horn of spinal cord-transected cats: differences in response to intravenous ketamine administered before and after formalin. *Acta Anaesthesiol Scand* 2000;44:953-8.

Reprint requests:

Dr. Cliff K. S. Ong
435 Orchard Road
Wisma Atria, Suite 11-02
Republic of Singapore
238877
cliffong@pacific.net.sg

CALL FOR REVIEW ARTICLES

The Journal encourages submission of topical review articles. These articles should be designed to review the current status of matters that are important to practitioners. These articles should contain current developments and changing trends, as well as reaffirmation of current techniques and policies.

Please consider submitting your article to appear as a Review Article. Information for authors appears in each issue of *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*.