A dose-response study of adrenaline combined with lignocaine 2%: effect on acute postoperative pain after oral soft tissue surgery

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Aims The combination of lignocaine and adrenaline may cause more postoperative pain than other types of local anaesthetic agents with comparable clinical efficacy. This study investigates the dose-response effect of adrenaline added to lignocaine on postoperative pain, when used as local anaesthetic for oral soft tissue surgery.

Methods A controlled, randomized, double-blind, parallel group study included 195 patients (108 females/87 males) with mean age 49 years (range 26–75 years). The patients were allocated to one of three treatment groups receiving lignocaine 2% ($n=66$), lignocaine 2% with adrenaline 1:160 000 ($n=63$) or lignocaine 2% with adrenaline 1:80 000 ($n=66$).

Results Lignocaine 2% with adrenaline 1:80 000 gave significantly more pain intensity than lignocaine 2% or lignocaine 2% with adrenaline 1:160 000. The postoperative pain intensity courses after lignocaine 2% and lignocaine 2% with adrenaline 1:160 000 showed a similar pattern except for the time period just after completion of surgery when lignocaine 2% with adrenaline 1:80 000 caused less pain.

Conclusions High adrenaline concentrations (1:80 000) combined with lignocaine local anaesthetic solution offers no advantage with respect to pain alleviation during the immediate postoperative pain period. High exogenous adrenaline concentrations may play a significant role in enhancing acute postoperative intensity.

Keywords: adrenaline, lignocaine, oral surgery, postoperative pain, VAS

Introduction

Local anaesthesia is probably the most widely used pain relieving technique for simple to more complex types of surgical interventions in both general medicine and dentistry. The most frequently addressed pharmacodynamic characteristic regarding local anaesthetics is clinical efficacy qualities such as latency time, incidence of successful anaesthesia and duration. Few researchers have addressed the possibility that some local anaesthetics may influence the postoperative pain course in a less advantageous way [1, 2].

In 1903 Braun demonstrated that the addition of adrenaline to local anaesthetic solutions greatly prolongs and intensifies their action [3]. However, the popular

combination of adrenaline (1:80 000) with lignocaine 2%, which supposedly offers the optimal combination regarding clinical efficacy variables, shows more postoperative pain than other local anaesthetic agents available in Scandinavia [4]. The purpose of this dose-response trial was to study the effects of varying adrenaline concentrations combined with lignocaine on acute postoperative pain intensity using oral soft tissue surgery as pain insult.

Methods

The trial was a controlled, randomized, double-blind, between-patient, parallel group trial using patients referred for gingivectomies to a specialist practice in periodontology. Patients who had achieved good oral hygiene after initial treatment, but had persistent bilateral areas of pathological pockets, were asked to volunteer for the study. Patients who presented gingival conditions necessitating treatment other than gingivectomies or who were considered unable to fill in a clinical record form (CRF) according to protocol, were not asked to participate.

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Informed consent was obtained from all subjects after the nature and the intentions of the study were explained to them. The trial protocol was approved (S-93078) by the Ethics Committee for Medical Research, Health Region II, Norway.

The patients were allocated to one of three possible treatment groups according to a randomized list on the visit for surgery. Prior to the first operation patients received plain lignocaine HCl 20 mg ml⁻¹ (LIG), lignocaine HCl 20 mg µl⁻¹ + adrenaline 6.25 µg ml⁻¹ (LIGA160) or lignocaine HCl 20 mg ml⁻¹ + adrenaline 12.5 µg ml⁻¹ (LIGA80). LIG and LIGA80 was commercially obtained in capped vials and came from the same manufacturer, Xylocain 2% and Xylocain Adrenalin (Astra, Södertälje, Sweden), respectively. LIGA160 was made according to the same pharmaceutical drug formulation as LIGA80 with the exception of the halved adrenaline concentration (Rikshospitalets Apotek, Oslo, Norway) supplied in capped vials identical to those bought from Astra. A person independent of the clinic relabelled the capped vials. The vials were marked 'treatment A' to 'treatment C' according to the codes used in the randomization list before usage. The colour of the solutions, and the shape and appearance of the vials, were similar except for the labelling stated above. Both the patients, the surgeon and assistants were blinded with respect to the type of local anaesthetic treatment given on each occasion.

Neither premedication nor topical anaesthetic was given to the patients before, during or after surgery. Local anaesthetic was infiltrated into the gingival areas destined for surgery with thin 27G × 1.5 in (0.4 × 0.4 mm), B. Braun Melsungen AG, Melsungen, FRG, hypodermic needles for dental use. The needle was inserted gently in one continuous movement to the gingival target area where the local anaesthetic solution was injected above the periosteum without scraping the periosteum. No significant leakage of local anaesthetic solution during infiltration was observed for any patient and successful infiltration was confirmed by transient tissue ischaemia. All injected volumes of local anaesthetic were noted. Surgery started 2 min after the anaesthetic injection. The same surgeon (LJ) carried out all the gingivectomies, without any bone removal, as outlined by Ramfjord & Ash [5]. Periodontal packs (Coe-pak, Coe Laboratories Inc., Chicago, IL, USA) were applied as wound dressings. Efforts were made to make the periodontal packs similar in shape and extension for all similar bilateral surgical areas. The time used from incision to finished periodontal pack was noted.

The patients received case report forms (CRF) on which they were instructed to assess their subjective postoperative pain intensity on visual analogue scales (VAS) running from 'no pain' (0 mm) to 'pain cannot be

worse' (100 mm). The assessments started when the surgical procedure was completed and continued hourly for the next 11 h. The sum pain intensity was calculated by adding the hourly VAS scores over the 11 h observation period.

The patients were instructed not to consume any alcohol during the 11 h observation period following surgery or to take any analgesic medication unless it was considered absolutely necessary. If any analgesic was taken, the time of drug intake, the number of tablets and type of medication was to be noted on the CRF. If any analgesic was taken, the pain score at the time of medication should represent the score until the end of the observation period. The patients returned to the clinic 14 days after each gingivectomy for removal of the periodontal packs and wound control. The CRFs were collected and the patients were asked if they had taken any analgesic drugs. The verbal answer to that question was checked with the patients' CRFs. Any wound complications were also noted.

All variables used for statistical analyses were checked for normality using the Kolmogorov-Smirnov test. The one-way ANOVA procedure with Scheffé's test for multiple comparisons was used for parametrically distributed data. Nonparametric data was first analysed with the Kruskal-Wallis *H*-test to find a statistically significant difference indicating a possible difference between the groups. If so, each possible independent pair of variables within the three treatment groups was compared with the Mann-Whitney *U*-test. The Chi-Square test was used to compare the observed and expected frequencies between groups where pertinent. The statistical package SPSS 8.0 for Windows [6] was used with a significance level of 5%.

Results

Two hundred and seventeen (122 females/95males) Norwegian patients of Caucasian origin with a mean age of 49 years (range 26–75 years) entered the study. Twenty-two patients were excluded from the trial. The reasons for exclusions were; LIG: five patients where four patients (four females) did not return CRFs and one (male) experienced complications during the surgery (bleeding requiring sutures), LIGA160: nine patients where seven patients (three female/four male) did not return the CRF and two patients experienced complications (one female/one male), and LIGA80 where eight patients (six females/two males) did not return their CRF. This left 195 patients (108 females/87 males) with mean age 49 years (range 26–75 years) for statistical analyses. Patient characteristics and descriptive details of the surgery for each treatment group are listed in Tables 1 and 2.

There were no statistically significant differences between mean age (one-way ANOVA, $P=0.52$), the female/male ratio (two-sided Chi-Square test, $P=0.89$) and the time

used for infiltration of local anaesthetic (Kruskal–Wallis *H*-test, $P=0.32$) within each treatment group. There was a statistically significant difference between the treatment groups with respect to volume of local anaesthetic used where the LIG group used a greater volume (Scheffé's test, $P<0.001$) than the LIGA160 and LIGA80 group. Furthermore, a tendency towards a statistically significant difference (Scheffé's test, $P=0.052$) between LIG and LIGA80 regarding the duration of surgery was seen. No other statistically significant associations were seen regarding the patients or surgical characteristics. There were no statistical significant differences between the specific localization of soft tissue areas subjected to surgery (Kruskal–Wallis *H*-test, $P>0.27$) or the total areas of surgical involvement (one-way ANOVA, $P>0.70$) between the treatment groups (Table 3).

The postoperative time courses of the mean acute postoperative pain intensity following LIG, LIGA160 and

LIGA80 are shown in Figure 1 and the data in Table 4. The mean postoperative pain intensity after LIG was numerically higher just after completion of surgery (0 h) compared with LIGA160 and LIGA80. This difference was statistically significant between LIG and LIGA160 ($P=0.001$). The difference tended to be significant between LIG and LIGA80 ($P=0.07$). The PI after LIGA160 was numerically lower than that after LIGA80 ($P=0.06$) at 0 h. At 1 h after surgery the PI after LIG was numerically higher ($P=0.05$) than that after LIGA160. Through the remaining observation period there was no statistically significant difference between the pain courses of LIG and LIGA160 (all $P>0.13$). LIGA80 distinguished itself by showing a significantly higher PI than both LIG and LIGA160 from 1 h after surgery to the end of the observation period (all timepoints $P<0.02$). The mean SPI scores for the whole observation period are presented in Table 3. LIG was not statistically different from LIGA160 ($P=0.80$), but different from LIGA80 ($P=0.001$). LIGA160 was different from LIGA80 ($P=0.002$).

The distribution of patients who did not experience pain *vs* those who did within each treatment group at each time-point is shown in Table 5. There was a numerical majority of patients experiencing no pain in both the LIG and LIGA160 groups compared with those being treated with LIGA80 as local anaesthetic. This difference was, however, only significant at 4 ($P<0.04$) and 9 ($P<0.02$) h after surgery (two-sided Chi-Square test). No patient in this study experienced lack of analgesic effect of the used local anaesthetics during the surgical procedures, although the first reports of pain were recorded just after completion of wound dressing. No postoperative wound complications were seen during this study.

A total of 17 patients took analgesics irrespective of treatment group during the observation period. After LIG,

Table 1 Demographic data of patients subjected to gingivectomies using lignocaine 2% (LIG), lignocaine 2% with adrenaline 1 : 160 000 (LIGA160) or lignocaine 2% with adrenaline 1 : 80 000 (LIGA80) as local anaesthetic.

	LIG vs LIGA160	LIGA160 vs LIGA80	LIG vs LIGA80	
<i>n</i>	66	63	66	
Age (years)	48 (31–70)	50 (26–72)	49 (32–75)	NS§
Ratio females/males	37/29	36/27	35/31	NS#
% females/males	56.1/43.9	57.1/42.9	53.0/47.0	–

Mean age (range) is shown. Significance level 5%. NS No statistically significant difference between any group. §Data analysed with one-way ANOVA, and Scheffé's test. #Data analysed with two-sided Chi-Square test.

Table 2 Description of surgical procedures in patients subjected to gingivectomies using lignocaine 2% (LIG), lignocaine 2% with adrenaline 1 : 160 000 (LIGA160) or lignocaine 2% with adrenaline 1 : 80 000 (LIGA80) as local anaesthetic. Data shown as differences (95% CI) between treatments.

	LIG vs LIGA160	LIGA160 vs LIGA80	LIG vs LIGA80	
LA volume (ml)	0.53§ (0.28, 0.79)	0.18 (–0.05, 0.41)	0.71§ (0.49, 0.94)	
LA infiltration time (min:s)	–00:06 (–00:20, 00:07)	00:06 (–00:07, 00:20)	00:00 (–00:07, 00:07)	NS‡
Duration of gingivectomy (min:s)	–00:47 (–01:55, 00:20)	–00:40 (–01:54, 00:34)	–01:27 (–02:38, –00:16)	NS+

NS No statistically significant difference between any group. Significance level 5%. §Significant difference ($P<0.05$) found with one-way ANOVA, and Scheffé's test. +Data analysed with one-way ANOVA, and Scheffé's test. ‡Data analysed with the Kruskal–Wallis *H*-test, and the two-tailed Mann–Whitney test.

Table 3 Specific and total surgical areas involved in gingivectomies performed on patients after using lignocaine 2% (LIG), lignocaine 2% with adrenaline 1 : 160 000 (LIGA160) or lignocaine 2% with adrenaline 1 : 80 000 (LIGA80) as local anaesthetic. Data shown as differences (95% CI) between treatments.

Areas involved in surgery	LIG vs LIGA160	LIGA160 vs LIGA80	LIG vs LIGA80	
Maxillary molars	-0.11 (-0.42, 0.20)	0.17 (-0.14, 0.48)	0.06 (-0.24, 0.36)	NS‡
Mandibular molars	0.10 (-0.07, 0.28)	-0.12 (-0.29, 0.06)	0.02 (-0.22, 0.19)	NS‡
Maxillary premolars	-0.04 (-0.38, 0.30)	0.15 (-0.18, 0.48)	0.11 (-0.22, 0.43)	NS‡
Mandibular premolars	0.09 (-0.19, 0.37)	0.02 (-0.24, 0.27)	0.11 (-0.15, 0.36)	NS‡
Maxillary incisors	-0.22 (-1.05, 0.61)	-0.58 (-1.48, 0.32)	-0.80 (-1.66, 0.06)	NS‡
Mandibular incisors	0.22 (-0.59, 1.03)	0.15 (-0.62, 0.91)	0.36 (-0.42, 1.15)	NS‡
Total number of teeth	0.04 (-0.52, 0.60)	-0.22 (-0.82, 0.37)	0.18 (-0.71, 0.35)	NS§

NS No statistically significant difference between any group. Significance level 5%. §Data analysed with one-way ANOVA, and Scheffé's test.

‡Data analysed with the Kruskal-Wallis *H*-test, and the two-tailed Mann-Whitney test.

Figure 1 Mean (s.e. mean) postoperative pain intensity scored on VAS by patients after gingivectomies using lignocaine 2% (●, *n*=66) or lignocaine 2% with adrenaline 1 : 160 000 (○ *n*=63) or lignocaine 2% with adrenaline 1 : 80 000 (▼, *n*=66) as local anaesthetic.

five patients (four females/one male) took analgesics (three patients took unknown analgesics, one patient took 500 mg paracetamol, 1 took 60 mg codeine phosphate + 1000 mg paracetamol). After LIGA160 six patients (five females/one male) took analgesics (one patient took 1000 mg paracetamol, three took 500 mg paracetamol, one patient took 30 mg codeine phosphate + 500 mg

Table 4 Mean pain intensity scores shown as differences (95% CI) between treatments assessed by patients on 100 mm VAS after gingivectomies using lignocaine 2% (LIG), lignocaine 2% with adrenaline 1 : 160 000 (LIGA160) or lignocaine 2% with adrenaline 1 : 80 000 (LIGA80) as local anaesthetic.

Time after surgery (h)	LIG vs LIGA160	LIGA160 vs LIGA80	LIG vs LIGA80
0	1.74‡ (0.47, 3.01)	-0.48 (-1.02, 0.07)	1.26 (-0.09, 2.60)
1	2.56 (0.53, 4.60)	-3.06‡ (-5.05, -1.08)	-0.50‡ (-3.22, 2.22)
2	1.12 (-1.51, 3.76)	-4.53‡ (-7.55, -1.52)	-3.41‡ (-6.94, 0.12)
3	-0.16 (-3.11, 2.79)	-3.79‡ (-7.13, -0.45)	-3.95‡ (-7.55, -0.35)
4	-1.09 (-4.31, 2.12)	-3.73‡ (-7.39, 0.07)	-4.82‡ (-8.28, -1.35)
5	-1.05 (-4.23, 2.14)	-3.66‡ (-7.48, 0.15)	-4.71‡ (-8.19, -1.24)
6	-0.50 (-3.72, 2.72)	-3.86‡ (-7.69, 0.04)	-4.36‡ (-7.80, -0.93)
7	-0.28 (-3.60, 3.05)	-4.13‡ (-8.20, 0.07)	-4.41‡ (-8.11, -0.71)
8	0.15 (-3.01, 3.30)	-4.43‡ (-8.37, -0.49)	-4.28‡ (-8.17, -0.40)
9	0.56 (-2.25, 3.37)	-3.99‡ (-7.63, -0.35)	-3.43‡ (-7.16, 0.30)
10	0.36 (-2.31, 3.03)	-3.08‡ (-6.49, 0.34)	-2.72‡ (-6.24, 0.81)
11	0.17 (-2.28, 2.61)	-2.78‡ (-5.84, 0.28)	-2.61‡ (-5.80, 0.57)
Sum PI	3.62 (-24.28, 31.52)	-40.66§ (-73.11, -8.22)	-37.05§ (-69.68, -4.41)

§Significant difference (*P*<0.05) found with one-way ANOVA, and Scheffé's test. ‡Significant difference (*P*<0.05) found with the Kruskal-Wallis *H*-test, and the two-tailed Mann-Whitney test.

paracetamol and one took 60 mg codeine phosphate + 1000 mg paracetamol). After LIGA80 six patients (six females) took analgesics (four patients took 1000 mg paracetamol, one took 500 mg paracetamol and one took 70 mg dextropropoxyphene + 400 mg paracetamol). There was no statistically significant difference between the treatment groups with respect to number of patients taking analgesics (*P*=0.92), sex distribution (*P*=0.53) and type of analgesic (*P*=0.10) using the two-sided Chi-Square test.

Discussion

The patients used vertically orientated 100 mm VAS to measure their subjective pain intensity during the 11 h observation period. The VAS has previously been used successfully to assess postoperative pain when comparing local anaesthetics in both dental and nondental types of

Table 5 Distribution of patients experiencing pain after gingivectomies using lignocaine 2% (LIG), lignocaine 2% with adrenaline 1 : 160 000 (LIGA160) or lignocaine 2% with adrenaline 1 : 80 000 (LIGA80) as local anaesthetic.

Time after surgery (h)	LIG		LIGA160		LIGA80	
	pain/total	(% pain)	pain/total	(% pain)	pain/total	(% pain)
0	50/66	(75.8)	61/63	(96.8)	58/66	(87.9)
1	42/66	(63.6)	49/63	(77.8)	35/66	(53.0)
2	45/66	(68.2)	42/63	(66.7)	26/66	(39.4)
3	47/66	(71.2)	36/63	(57.1)	25/66	(37.9)
4	47/66	(71.2)	38/63	(60.3)	25/66	(37.9)#
5	45/66	(68.2)	40/63	(63.5)	26/66	(39.4)
6	43/66	(65.2)	40/63	(63.5)	24/66	(36.4)
7	45/66	(68.2)	42/63	(66.7)	25/66	(37.9)
8	45/66	(68.2)	44/63	(69.8)	26/64	(40.6)
9	46/66	(69.7)	49/62	(79.0)	29/63	(46.0)#
10	47/65	(72.3)	50/62	(80.6)	32/63	(50.8)
11	52/65	(80.0)	50/62	(80.6)	39/63	(61.9)
Sum	34/66	(51.5)	30/63	(47.6)	20/66	(30.3)

#Significant ($P < 0.05$) difference in the ratio of pain responders/no-pain responders found with two-sided Chi-Square test ($P < 0.04$) in the LIGA80 group compared with the other groups.

surgical procedures [7–10]. No statistically significant difference has been demonstrated between vertically and horizontally orientated VAS used to assess acute postoperative pain intensity [11]. The VAS has been compared with other types of frequently used pain scales with the majority of those studies stating superiority of the VAS [12–18]. The ability of the VAS to measure smaller changes in drug effects than other scales is important in a pain model such as ours presenting mild postoperative pain [19].

The present study demonstrates an unequivocal dose-response relationship between the adrenaline concentrations and the postoperative pain courses following the oral soft surgery. From these results it can be inferred that exogenously administered adrenaline possesses pain inducing capabilities when injected to innervated tissue areas. Adrenaline is a sympathomimetic amine which is known to exert its effect by functional interaction with adrenergic receptors. Adrenaline is known to act as an α - and β -receptor agonist on a multitude of metabolic and physiological actions [20], while less is known about its actions regarding nociception and pain transmission.

Adrenaline is a localizing agent added to local anaesthetics to delay their absorption velocity from the site of injection [21]. This effect is achieved through a vasoconstrictor action caused by local α_1 -receptor stimulation of the smooth muscles of peripheral vessels [22]. The consequence of this action is reduced tissue perfusion with reduced oxygen availability easily seen as clinical ischaemia of the tissue. Locally administered adrenaline may further give rise to local increase in oxygen consumption [23].

Acute postoperative inflammation involves a complex set of local cellular, biochemical and neuronal reactions [24] causing hyperalgesia, and nociception finally terminating in the central sensation leading to the subjective pain experience. Several hypotheses regarding the role of adrenaline may be discussed. It is generally believed, although questioned by others [25], that mechanisms involved in nociception are mediated by increases in cAMP [26, 27]. Tissue ischaemia elevates experimentally pig skin cAMP [28]. Adrenaline, but not lignocaine 2%, elevates cAMP levels in gingival tissues [29]. The effect of cellular cAMP, and tissue ischaemia allowing accumulation of pro-algesic mediator substances [30] within the area of tissue surgery may facilitate nociception following adrenaline injection.

Adrenaline plays an important part in the neurogenic component of inflammation [31] where it produces hyperalgesia, but only in the presence of tissue injury [32]. The periodontium (e.g. the soft tissue surrounding the teeth) is supplied with nerves which include sensory fibres from the end branches of the trigeminal nerve [33]. Normally primary afferent neurones do not have catecholamine sensitivity, but if pain receptive C-fibres are sensitised, noradrenaline is capable of further sensitisation [34]. Agonists that stimulate β -adrenergic receptors without the presence of specific α -adrenoceptor agonists appear to enhance the neuronal release of noradrenaline [20]. The sympathetic-/primary afferent-neurone interaction is mediated by α_2 -adrenoreceptors as demonstrated experimentally in animals [35]. As adrenaline is a non-specific adrenergic receptor agonist it is possible that a direct receptor-mediated pharmacodynamic effect which

contributes to hyperalgesia and, subsequently, pain is caused by the addition of adrenaline local anaesthetic agents.

The mean postoperative pain courses observed in the present study show distinct patterns. The patients in the treatment groups containing adrenaline, irrespective of concentration, started the observation period with no or almost no pain. The treatment group containing no adrenaline at all showed a mean pain intensity score more than 0 mm. These observations at 0 h may only reflect the duration of the local anaesthetics during the period of surgery. This is not consistent with the observation that the mean pain intensity of the treatment group receiving LIG only after a higher start more or less evens out with the pain intensity seen after LIGA160 treatment at 3 h and throughout the observation period. The mean pain intensity after LIGA80 starts at about the same level as LIGA160 but rapidly increases to give a higher pain intensity than the two other treatment groups throughout the observation period.

Although our study was controlled, double-blind, and randomized, the volumes of local anaesthetics were different between the groups. The duration of surgery tended also to be different between the treatments. The speculation that the larger volume of local anaesthesia used in the LIG group would enhance the pain relieving effect contrasts with the significantly higher pain score at 0 h after surgery. It has been proposed that the duration of surgical procedures may influence the postoperative pain intensity [36]. These studies have examined considerably longer time periods than those in our study and are contradicted by others [37]. We believe it is highly unlikely that the effect of LIGA80, which clearly differs from the two other treatment groups, can be explained by the mean surgical duration which was about 1.5 to 0.5 min longer with LIGA80 than the two other treatment groups.

The total pain experience seen in this model is of a relative low intensity, but is sufficient to allow for statistically significant discrimination between local anaesthetic agents of similar duration. The commonly used pain models, with more extensive bone and tissue damage, may provide a postoperative pain intensity which is too intense for studying the effects of local anaesthetic agents on postoperative pain intensity. It is concluded that exogenous adrenaline with a primary intended pharmacodynamic action to improve the clinical efficacy of local anaesthetic agents, possesses a pain inducing potential influencing acute postoperative pain.

References

- Oikarinen VJ, Ylipaavalniemi P, Evers H. Pain and temperature sensation related to local analgesia. *Int J Oral Surg* 1975; **4**: 151–156.
- Jorkjend L, Skoglund LA. Effect of non-eugenol- and eugenol-containing periodontal dressings on the incidence and severity of pain after periodontal soft tissue surgery. *J Clin Periodontol* 1990; **17**: 341–344.
- Braun H. Über den Einfluss der Vitalität der Gewebe auf die örtlichen und allgemeinen Giftwirkung lokaler anästhesierender Mitteln und über die Bedeutung des Adrenalins für die Lokalanesthäsie. *Arch Klin Chir* 1903; **69**: 541–591.
- Skoglund LA, Jorkjend L. Postoperative pain experience after gingivectomies using different combinations of local anaesthetic agents and periodontal dressings. *J Clin Periodontol* 1991; **18**: 204–209.
- Ramfjord SP, Ash MM. *Periodontology and Periodontology*. Philadelphia, W.B. Saunders, 1979: 543–556.
- Norusis MJ. *SPSS 8.0 guide to data analysis*. Upper Saddle River NJ, Prentice-Hall, 1998.
- Linden ET, Abrams H, Matheny J, Kaplan AL, Kopczyk RA, Jasper SJ. A comparison of postoperative pain experience following periodontal surgery using two local anesthetic agents. *J Periodontol* 1986; **57**: 637–642.
- Rosenquist JB, Nystrom E. Long-acting analgesic or long-acting local anesthetic in controlling immediate postoperative pain after lower third molar surgery. *SAAD Digest* 1987; **6**: 273–279.
- Rosivack GR, Koenigsberg SR, Maxwell KC. An analysis of the effectiveness of two topical anesthetics. *Anesth Prog* 1990; **37**: 290–292.
- Vickers ER, Punnia-Moorthy A. A clinical evaluation of three topical anaesthetic agents. *Aus Dental J* 1992; **37**: 266–270.
- Breivik EK, Skoglund LA. Comparison of present pain intensity assessments on horizontally and vertically oriented visual analogue scales. *Meth Find Exp Ther Pharmacol* 1998; **20**: 719–724.
- Joyce CR, Zutish DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. *Eur J Clin Pharmacol* 1975; **8**: 415–420.
- Stubbs DF. Visual analogue scales. *Br J Clin Pharmacol* 1979; **7**: 124.
- Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. *Ann Rheum Dis* 1978; **37**: 378–381.
- Huskisson EC. Visual analogue scales. In *Pain Management and Assessment*, ed. Melzack R. New York, Raven Press, 1983: 33–37.
- Carlsson AM. Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale. *Pain* 1983; **16**: 87–101.
- Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Metha G. Studies with different types of visual analogue scales for measurement of pain. *Clin Pharmacol Ther* 1983; **34**: 234–239.
- Seymour RA, Blair GS, Wyatt FAR. Postoperative dental pain and analgetic efficacy. *Br J Oral Surg* 1983; **21**: 290–297.
- Wallenstein SL. Commentary. The VAS relief scale and other analgesic measures. Carryover effect in parallel and crossover studies. *Adv Pain Res* 1991; **18**: 97–103.
- Weiner N. Norepinephrine, epinephrine, and the sympathomimetic amines. In *The Pharmacological Basis of*

- Therapeutics*, sixth edition, eds. Gilman AG, Goodman LS, Gilman A. New York. Macmillan Publishers Co Inc., 1980: 138–175.
- 21 Jage J. Circulatory effects of vasoconstrictors combined with local anesthetics. *Anesth Pain Contr Dent* 1993; **2**: 81–86.
 - 22 Knoll-Köhler E. Sicherheit bei der Lokalanästhesie. II. Pharmakologie vasokonstriktorischer Zusätze. *Phillip J* 1988; **15**: 79–89.
 - 23 Klingenström E, Westermark L. Local tissue-oxygen tension after adrenaline, noradrenaline and octapressin in local anaesthesia. *Acta Anaesthesol Scand* 1964; **8**: 261–266.
 - 24 Dale MM, Foreman JC. *Textbook of Immunopharmacology*, 2nd edn. Oxford. Blackwell Scientific Publications, 1989: 384
 - 25 Kumazawa T, Mizumura K, Koda H. Different mechanisms (receptor subtypes, second messenger actions) implicated in PGE 2-induced sensitization of the responses to bradykinin, to heat of polymodal receptors. In *Proceedings of the 7th World Congress on Pain*, eds. Gebhart GF, Hammond DL, Jensen TS. *Prog Pain Res Manag* 1994; **2**: 265–276.
 - 26 Ferreira SH. Peripeherial analgesia: mechanism of the analgesic action of aspirin like drugs and opiate-antagonists. *Br J Clin Pharmacol* 1980; **10**: 237S–245S.
 - 27 Ferreira SH. Inflammatory pain, prostaglandin hyperalgesia and the development of peripheral analgesics. *Trends Pharmacol Sci* 1981; **2**: 183–186.
 - 28 Yoshikawa K, Adachi K, Halprin KM, Levine V. Cyclic AMP in skin: effects of acute ischaemia. *Br Dent J* 1975; **92**: 249–254.
 - 29 Grower MF, Chandler D, Kramer G, Stow JA. Effects of local anesthesia on gingival cAMP levels. *J Periodontol* 1979; **50**: 38–42.
 - 30 Lim RKS. Pharmacological viewpoint of pain and analgesia. In *New Concepts in Pain and its Clinical Management*, ed. Way EL. Philadelphia, FA Davis, 1967: 33–47.
 - 31 Heller PH, Green PG, Tanner KD, Miao FJP, Levine JD. Peripheral neural contributions to inflammation. In *Progress in Pain Management*, Vol 1, eds Fields HL, Liebskind JC. Seattle, IASP Press, 1994: pp 31–42.
 - 32 Taiwo YO, Levine JD. Direct cutaneous hyperalgesia induced by adenosine. *Neuroscience* 1990; **38**: 757–762.
 - 33 Lindhe J, Karring T. The anatomy of the periodontium. In *Textbook of Clinical Periodontology* 1st edn, ed. Lindhe J. Copenhagen, Munksgaard, 1983: 19–65.
 - 34 Baron R. Pain memories: short and long-term alterations in CNS function after tissue inflammation and pain. *Dolor* 1998; **13**(Suppl 3): 9–17.
 - 35 Sato J, Suzuki S, Iseki T, Kumazawa T. Adrenergic excitation of cutaneous nociceptors in chronically inflamed rats. *Neurosci Lett* 1993; **164**: 225–228.
 - 36 Curtis JW, McLain JB, Hutchinson RA. The incidence and severity of complications and pain following periodontal surgery. *J Periodontol* 1985; **56**: 397–601.
 - 37 Seymour RA, Blair GS, Wyatt FAR. Post-operative dental pain and analgesic efficacy. Part 1. *Br J Oral Surg* 1983; **21**: 290–297.