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Comparison of lidocaine/tetracaine cream and lidocaine/prilocaine cream for local anaesthesia during laser treatment of acne keloidalis nuchae and tattoo removal: results of two randomized controlled trials

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Summary

Background Pain is a common adverse effect of dermatological laser procedures. Currently, no standard topical anaesthetic cream exists for deeper dermal laser procedures.

Objectives To compare the efficacy of lidocaine/tetracaine cream and lidocaine/prilocaine cream in reducing self-reported pain during deeper dermal laser treatment of acne keloidalis nuchae (AKN) and tattoos.

Methods We conducted two randomized, double-blind, controlled clinical trials with intrapatient, split-lesion designs: study A included patients with AKN (n = 15); study B included patients with black tattoos (n = 15). The primary end point was the patients' self-reported pain on a 10-cm visual analogue scale (VAS). Secondary objectives were the percentage of patients with adequate pain relief, willingness to pay €25 for the cream that provided the best pain relief and safety of the creams.

Results In both studies, VAS scores were lower for lidocaine/prilocaine cream, with a mean VAS difference in study A of 1·9 [95% confidence interval (CI) 1·0–2·8] and in study B of 0·6 (95% CI −0·7 to 1·9). In study A, adequate pain relief was achieved in 13% (n = 2) with lidocaine/tetracaine cream vs. 73% (n = 11) with lidocaine/prilocaine cream (P = 0·004), and in study B in 53% (n = 8) vs. 80% (n = 12), respectively (P = 0·289). In study A, 47% (n = 7) were willing to pay an additional €25 vs. 73% (n = 11) in study B. No serious adverse events occurred.

Conclusions Lidocaine/prilocaine cream under plastic occlusion is the preferred topical anaesthetic during painful laser procedures targeting dermal chromophores.

What's already known about this topic?

- Pain is a common adverse effect during dermatological laser procedures, which can be alleviated using a topical anaesthetic cream.

What does this study add?

- Lidocaine/tetracaine self-occlusive cream was not superior to lidocaine/prilocaine cream under plastic occlusion in reducing self-reported pain during laser treatment of acne keloidalis nuchae and tattoo removal.
- Lidocaine/prilocaine cream under occlusion is the preferred topical anaesthetic during laser procedures when targeting dermal chromophores.

Pain is a common and bothersome adverse effect of dermatological laser procedures. To prevent thermal damage to the epidermis and to alleviate laser-induced pain, most laser devices use simultaneous local skin cooling. However, local cooling often does not provide adequate pain relief. In such cases, local anaesthetics can be used to reduce procedure-related pain and increase patient satisfaction. Anaesthetics inhibit the sensory input to the central nervous system by blocking voltage-gated sodium channels.[1] The blockade of sodium influx prevents action potentials and inhibits nerve cell depolarization. B fibres (myelinated autonomic preganglionic fibres) are blocked first, followed by C fibres (nonmyelinated fibres) and, finally, A fibres (myelinated somatic fibres), which regulate pain and temperature.[2,3]

Injectable anaesthetics can be painful to administer and cannot be used in patients with needle phobia. Topical anaesthetics may be an alternative option. One of the most widely used products is an eutectic mixture of 2·5% lidocaine and 2·5% prilocaine cream (EMLA®, AstraZeneca, London, U.K.; henceforth referred to as 'LP cream'). A practical disadvantage of LP cream is the need for it to be applied under plastic occlusion. A recently (re)introduced topical anaesthetic, which contains the highest concentration of active anaesthetic ingredients available in a Food and Drug Administration-approved topical cream, is an eutectic mixture of 7% lidocaine and 7% tetracaine cream (Pliaglis®, Galderma Laboratories, Fort Worth, TX, U.S.A.; henceforth referred to as 'LT cream'). As LT cream forms a self-occlusive film when exposed to air, it is said to not require plastic occlusion. LT cream has shown superiority over placebo in pain reduction during several dermatological laser procedures,[4–7] and lower pain scores compared with LP cream during (superficial) single-pass CO_2 laser skin resurfacing.[8] However, apart from this single study, no head-to-head studies have been performed for other dermatological indications or laser systems. It is therefore unknown whether LT cream is also superior to LP cream in providing anaesthesia when targeting dermal chromophores.

Two examples of common indications for laser treatment in dermatology which require deeper dermal anaesthesia are hair removal, such as in acne keloidalis nuchae (AKN), and tattoo removal. AKN is a chronic, scarring folliculitis in which hair follicles are the principle contributors to inflammation.[9] Laser-assisted hair removal causes coagulation necrosis of the viable hair follicles and hair shafts in the deep dermis, and has shown positive results for AKN.[10,11] In tattoos, using nanosecond Q-switched laser pulses, the ink particles are fragmented into smaller pieces, which can then be phagocytosed by macrophages and cleared from the skin via the lymph vessels to the draining lymph nodes.[12]

The aim of this study was to evaluate the efficacy of LT cream compared with LP cream in reducing self-reported pain during laser treatments of AKN (study A) and tattoos (study B).

Patients and methods

Study population

Eligible for inclusion in study A were patients aged ≥ 18 years with AKN, and eligible for inclusion in study B were those aged ≥ 18 years with a black, professionally placed tattoo. Key exclusion criteria for both studies included known hypersensitivity or contact allergy to any components of the test materials, use of any other pain medication 24 h prior to the study visit, pregnant or breastfeeding women, and damaged skin at the designated treatment area.

Study design and randomization

These double-blind, randomized, controlled trials with intrapatient, split-lesion design were approved by the medical ethical review board of the Erasmus Medical Centre (MEC-2014-517; 14-11-2014) and registered at ClinicalTrials.gov (NCT02372786). All patients provided written informed consent before study participation. Both studies were of single-centre design and all patients were treated at the Erasmus University Medical Centre in Rotterdam, the Netherlands.

Study design and treatment protocols were similar for both studies. The treatment areas (i.e. necks in study A, and tattoos in study B) were divided into two equal, anatomically similar treatment sides (left and right). Both sides were separated by an area of 1 cm, which was left untreated, to avoid possible spill over effects of the two anaesthetic creams. Both creams were applied to each patient, and the order of cream application was randomized. A computer-generated randomization list was provided by the department of Biostatistics of the Erasmus Medical Centre, and was only available to the unblinded study nurse. The creams were applied by our unblinded study nurse according to the manufacturer's instructions and according to randomization. LT cream dried when exposed to air (self-occlusive), and LP cream was applied under occlusion using an occlusive plastic film (Fig. 1). The creams were removed by the unblinded study

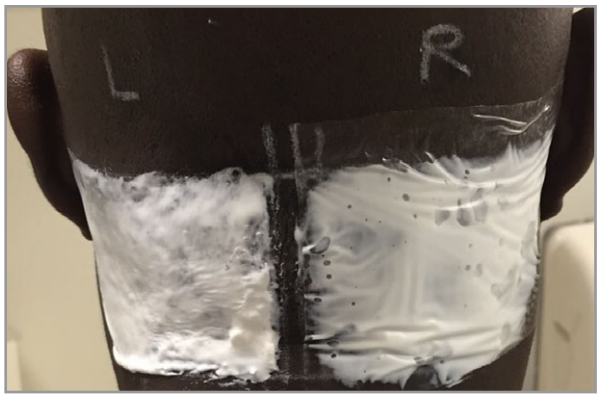

Fig 1. Application of lidocaine/tetracaine (LT) cream (self-occluding) on the left treatment side and lidocaine/prilocaine (LP) cream under plastic occlusion on the right treatment side in a patient with acne keloidalis nuchae.

nurse after 60 min, after which the patient was transferred to the laser treatment room. The skin was then examined by the blinded investigator and any local reactions were recorded. All laser procedures were started within 5 min of removal of the anaesthetic creams. In all cases, the laser treatment began on the left treatment side followed by the right treatment side, to minimize any potential order effect. Immediately after laser treatment of each side, pain scores were assessed using a standard 10-cm visual analogue scale (VAS), with lower scores indicating less pain.

One week after the visit, all patients were contacted by telephone, to assess potential adverse events after treatment.

Laser treatment

Laser settings were determined based on the safe clinical responses to previously performed test spots. Test spots are part of the normal routine procedure in our daily clinical practice, and were executed before study participation.

Study A (acne keloidalis nuchae)

The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (Cynosure Cynergy, Westford, MA, U.S.A.) emitting a wavelength of 1064 nm was used for hair removal in patients with AKN. A spot size of 7 or 10 mm, fluences of between 35 and 60 J/cm^2, pulse duration of 25 ms and frequency of 1 Hz were used. Two passes were applied. Standardized air-cooling (Zimmer Air Cooler; Zimmer, Irvine, CA, U.S.A.) was administered during treatment for thermal protection of the epidermis, and additional pain relief, whereby both sides were (pre)cooled in an identical manner.

Study B (tattoos)

A Q-switched Nd:YAG laser (Quanta Systems, Solbiate Olona, Italy), emitting a wavelength of 1064 nm was used for tattoo removal. A spot size of 3 mm, fluences of between 6 and 10 J/cm^2 and a frequency of 1 Hz were used. A single pass was applied.

Study objectives

The primary objective of both studies was to compare the efficacy of LT cream and LP cream in reducing self-reported pain, using a 10-cm VAS, during a single laser procedure. Secondary objectives of both studies were to evaluate the percentage of patients who reported adequate pain relief (yes/no), to monitor the nature and frequency of adverse events, and to evaluate if patients were willing to pay approximately €25 for the treatment that provided superior pain reduction. This last question was included as LP cream is, in the Netherlands, reimbursed by health insurance and LT cream has to be purchased for approximately €25 (per 15 g).

Statistical analysis

For both studies, a sample size of 15 patients was calculated to provide 80% power to detect a difference of 2 (SD 2·5) in the VAS, which is determined to be (approximately) the minimal clinically important difference that a patient can detect,[13] with a two-sided type I error level of 5%. A t-test for paired samples was used.

The results of the two studies were analysed separately. The differences in VAS scores between the LT and LP creams were analysed using a t-test for paired samples. Normality of the variables was tested using a Shapiro–Wilk test. The differences between LT and LP cream regarding adequate pain relief were analysed using a McNemar test. The side on which the treatment was least painful and willingness to spend approximately €25 for the cream used on this side are shown as percentages and absolute numbers of cases. P-values $< 0{\cdot}05$ were considered statistically significant. SPSS Statistics 21 (IBM, Armonk, NY, U.S.A.) was used for all analyses.

Results

Between February and September 2015, a total of 15 patients were enrolled in study A (AKN), and between February and July 2015, a total of 15 patients were enrolled in study B (tattoos). Patient demographics are shown in Table 1. There were no dropouts or exclusions after randomization in both studies.

Table 1 Patient demographics

	Study A (AKN)	Study B (tattoos)
Patients (n)	15	15
Sex (n)		
Male	15	5
Female	0	10
Mean ± SD age (years)	41 ± 12	39 ± 10
Fitzpatrick skin type (n)		
I	–	1
II	–	7
III	1	3
IV	2	1
V	9	3
VI	3	0
Previous laser treatments (n%)		
No	15 (100)	7 (47)
Yes	–	8 (53)
Mean number of previous treatments	–	5
Localization (n)		
Face	–	1
Neck	15	1
Chest	–	1
Upper extremities	–	10
Lower extremities	–	2

AKN, acne keloidalis nuchae.

Study A: acne keloidalis nuchae

The mean ± SD VAS scores were 5·5 ± 1·7 for LT cream and 3·7 ± 2·6 for LP cream (Fig. 2), with a mean VAS difference of 1·9 [95% confidence interval (CI) 1·0–2·8; P = 0·001].

Adequate pain relief during the laser procedure was achieved in 13% (n = 2) of the patients receiving LT cream and 73% (n = 11) of the patients receiving LP cream (P = 0·004) (Fig. 3).

Seven per cent (n = 1) rated the side treated with LT cream as least painful vs. 80% (n = 12) of the patients receiving LP cream. Thirteen per cent (n = 2) of the patients did not have a preference for either side. Of all patients, 47% (n = 7) were willing to pay €25 for future treatment with the cream that provided the best pain relief.

Study B: tattoos

The mean ± SD VAS scores were 4·3 ± 1·8 for LT cream and 3·7 ± 2·3 for LP cream (Fig. 4). The mean VAS difference of 0·6 (95% CI −0·7 to 1·9; P = 0·335) was not statistically significant.

Adequate pain relief during the laser procedure was achieved in 53% (n = 8) of the patients with LT cream and 80% (n = 12) of the patients with LP cream (P = 0·289) (Fig. 5).

Of all patients, 33% (n = 5) rated the side treated with LT cream as least painful vs. 60% (n = 9) of the patients for LP cream. Seven per cent (n = 1) of the patients did not have a preference for either side. Of all patients, 73% (n = 11) were willing to pay €25 for future treatment with the cream that provided the best pain relief.

Local reactions and adverse events of both studies

During examination of the skin immediately after cream removal, the side treated with LT cream showed blanching in 0%, oedema in 20% (n = 3) and erythema in 27% (n = 4) in

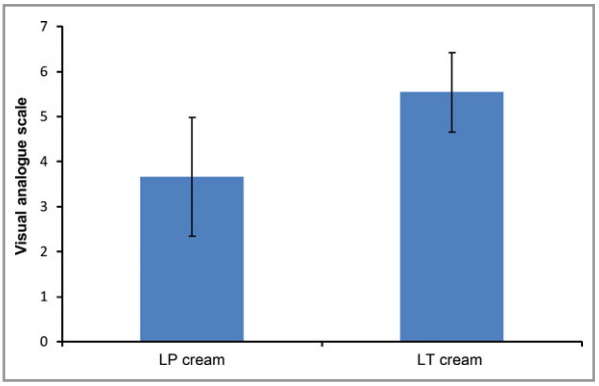

Fig 2. Study A: patients with acne keloidalis nuchae (n = 15). Visual analogue scale scores after application of lidocaine/tetracaine (LT) cream (self-occluding) on one treatment side and lidocaine/prilocaine (LP) cream under plastic occlusion on the other treatment side (P = 0·001).

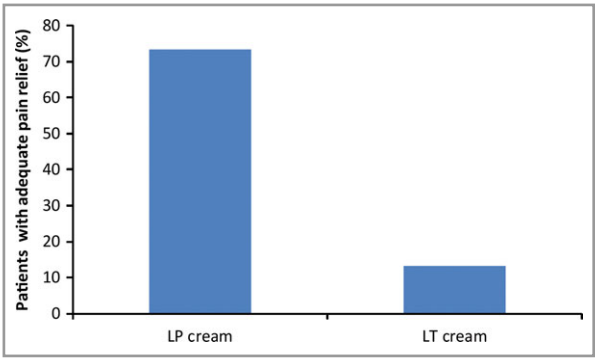

Fig 3. Study A: patients with acne keloidalis nuchae (n = 15). Percentage of patients who perceived adequate pain relief after application of lidocaine/tetracaine (LT) cream (self-occluding) on one treatment side and lidocaine/prilocaine (LP) cream under plastic occlusion on the other treatment side (P < 0·004).

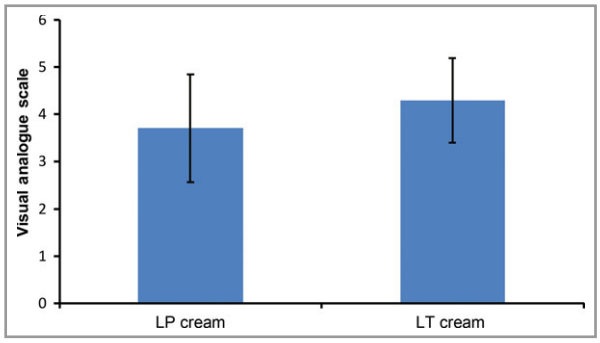

Fig 4. Study B: patients with tattoos (n = 15). Visual analogue scale scores after application of lidocaine/tetracaine (LT) cream (self-occluding) on one treatment side and lidocaine/prilocaine (LP) cream under plastic occlusion on the other treatment side (P = 0·335).

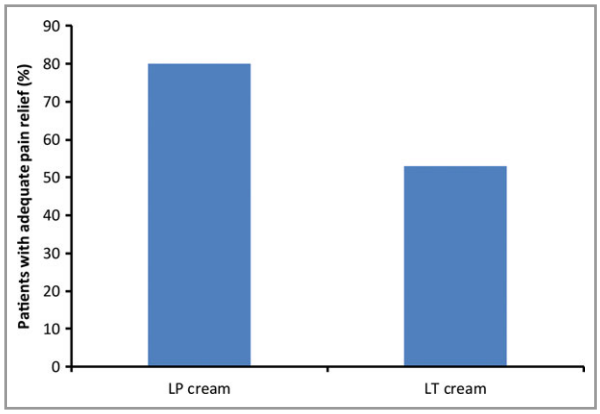

Fig 5. Study B: patients with tattoos (n = 15). Percentage of patients who perceived adequate pain relief after application of lidocaine/tetracaine (LT) cream (self-occluding) on one treatment side and lidocaine/prilocaine (LP) cream under plastic occlusion on the other treatment side (P = 0·289).

study A, and blanching in 0%, oedema in 13% (n = 2) and erythema in 53% (n = 8) in study B. On the side treated with LP cream no local reactions were seen after cream removal in study A, and in study B blanching was seen in 47% (n = 7), oedema in 7% (n = 1) and erythema in 0% of the patients. These local reactions were all mild and transient.

Thirteen patients in study A and 13 in study B were available for telephone consultation 1 week after treatment. In study A, two patients reported adverse events: burning sensation (n = 1), and itching and crusting (n = 1). In study B, five patients reported adverse events: swelling (n = 1), itching (n = 2) and mild blistering (n = 2). All adverse events were transient and most likely related to the laser treatments. No serious adverse events occurred.

Discussion

The main finding of study A was that LP cream provided statistically significant lower pain scores than LT cream during the Nd:YAG laser treatment of AKN. Previous studies defined the minimal clinically important difference (i.e. the smallest clinically relevant change that a patient can detect) on a 100-mm VAS to be between 9 and 18 mm.[13,14] Thus, the statistically significant 19-mm VAS difference we found between the two creams during AKN treatment (favouring LP cream) is also clinically relevant.

The results of study B showed no significant differences between the two creams in reducing self-reported pain during the Q-switched Nd:YAG laser treatment of tattoos, although the numerical difference appears to be in favour of LP cream. Possibly, the lack of statistical significance in this study, compared with study A, is caused by the fact that laser-assisted hair removal in AKN is more painful than tattoo removal. Breivik *et al.* showed that the power to detect a difference in pain intensity is higher when there is a large difference and a higher baseline pain.[15,16] Terminal hair follicles are located deeper in the dermis than tattoo ink particles and, together with the larger spot size and higher fluence (causing more volumetric bulk heating of the dermis), treatment with a long-pulsed Nd:YAG laser for hair removal is associated with more (painful) thermal injury to the skin than the ultrashort-pulsed Nd:YAG laser used for tattoo removal. Also, in laser tattoo removal there is less of a photothermal and more of a photoacoustic effect, which is less painful. Additionally, the AKN group was very homogeneous, whereas the tattoo group was more heterogeneous, including various anatomical locations, sexes, skin types and number of previous laser treatments. These are all factors that could have increased the variability and therefore have influenced the statistical significance of the results.

The results appear to be in contrast with the only published head-to-head study which reported self-occluding LT cream to be superior to LP cream under occlusion, after a 30-min application time, during single-pass CO_2 laser skin resurfacing.[8] However, it might not be possible to extrapolate the results found during this superficial laser treatment to treatments with longer wavelength lasers used for both AKN and tattoo removal. Longer wavelength lasers penetrate much deeper into the dermis, triggering far more nerves than a single-pass CO_2 laser skin ablation. Furthermore, as the label-recommended application time for LP cream is a minimum of 60 min (https://www.medicines.org.uk), the results of Alster and Lupton may have been influenced by the shorter application time of only 30 min.[8]

The effectiveness of an anaesthetic cream mainly depends on the rate of (trans)dermal absorption. This absorption rate is determined by the thickness of the stratum corneum, and the pKa (acid dissociation constant) of the anaesthetic.[2] Penetration through the skin can be enhanced by occlusion, which increases temperature and hydration of the stratum corneum. The thinner the stratum corneum and the closer the pKa matches the pH of the skin (~5·5),[17] the better the anaesthetic penetrates through the skin. As every patient in both of our studies was his or her own control, the thickness of the stratum corneum was equal for both treatment sides. Both creams contained lidocaine (pKa 7·7), and the pKa of prilocaine and tetracaine did not differ substantially (7·9 and 8·6, respectively).[18] Therefore, the main factor that could have made a difference in (trans)dermal absorption between the two creams is the different method of occlusion. The flexible film formed by LT cream might not have facilitated optimal drug absorption and, despite its higher concentrations of anaesthetics, provided less (deeper) dermal pain reduction.

Besides pain reduction, potential side-effects, costs and ease of use should be taken into account when choosing an anaesthetic cream. Mild local reactions were observed after cream removal, but no clinically important differences between the two creams were evident. In the Netherlands, the retail price of LT cream is approximately 2·5 times higher than that of LP cream, and LT cream is not reimbursed by health insurance. In our experience, LT cream was easier to apply but sometimes difficult to remove. On the contrary, LP cream was more difficult to apply using plastic occlusion but easier to remove.

Limitations of both studies were the relatively small sample sizes, and that patients were not completely blinded as the methods of occlusion were different. However, it was assumed patients did not know which method belonged to which cream.

In summary, we conclude that a 60-min application of LP cream under plastic occlusion is the preferred topical anaesthetic during painful laser procedures targeting dermal chromophores.

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References

1 Meechan JG. Intraoral topical anesthesia. *Periodontol* 2000 2008; **46**:56–79.
2 Sobanko JF, Miller CJ, Alster TS. Topical anesthetics for dermatologic procedures: a review. *Dermatol Surg* 2012; **38**:709–21.

3 Kaweski S; Plastic Surgery Educational Foundation Technology Assessment Committee. Topical anesthetic creams. *Plast Reconstr Surg* 2008; **121**:2161–5.
4 Chen JZ, Alexiades-Armenakas MR, Bernstein LJ *et al.* Two randomized, double-blind, placebo-controlled studies evaluating the S-Caine Peel for induction of local anesthesia before long-pulsed Nd:YAG laser therapy for leg veins. *Dermatol Surg* 2003; **29**:1012–18.
5 Jih MH, Friedman PM, Sadick N *et al.* 60-minute application of S-Caine Peel prior to 1,064 nm long-pulsed Nd:YAG laser treatment of leg veins. *Lasers Surg Med* 2004; **34**:446–50.
6 Chen JZ, Jacobson LG, Bakus AD *et al.* Evaluation of the S-Caine Peel for induction of local anesthesia for laser-assisted tattoo removal: randomized, double-blind, placebo-controlled, multicenter study. *Dermatol Surg* 2005; **31**:281–6.
7 Alster T, Garden J, Fitzpatrick R *et al.* Lidocaine/tetracaine peel in topical anesthesia prior to laser-assisted hair removal: Phase-II and Phase-III study results. *J Dermatolog Treat* 2014; **25**:174–7.
8 Alster TS, Lupton JR. Evaluation of a novel topical anesthetic agent for cutaneous laser resurfacing: a randomized comparison study. *Dermatol Surg* 2002; **28**:1004–6.
9 Herzberg AJ, Dinehart SM, Kerns BJ, Pollack SV. Acne keloidalis. Transverse microscopy, immunohistochemistry, and electron microscopy. *Am J Dermatopathol* 1990; **12**:109–21.
10 Shah GK. Efficacy of diode laser for treating acne keloidalis nuchae. *Indian J Dermatol Venereol Leprol* 2005; **71**:31–4.
11 Esmat SM, Abdel Hay RM, Abu Zeid OM, Hosni HN. The efficacy of laser-assisted hair removal in the treatment of acne keloidalis nuchae; a pilot study. *Eur J Dermatol* 2012; **22**:645–50.
12 Choudhary S, Elsaie ML, Leiva A, Nouri K. Lasers for tattoo removal: a review. *Lasers Med Sci* 2010; **25**:619–27.
13 Todd KH, Funk JP. The minimum clinically important difference in physician-assigned visual analog pain scores. *Acad Emerg Med* 1996; **3**:142–6.
14 Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? *Acad Emerg Med* 1998; **5**:1086–90.
15 Breivik EK, Bjornsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain* 2000; **16**:22–8.
16 Breivik H, Borchgrevink PC, Allen SM *et al.* Assessment of pain. *Br J Anaesth* 2008; **101**:17–24.
17 Braun-Falco O, Korting HC. [Normal pH value of human skin]. *Hautarzt* 1986; **37**:126–9 (in German).
18 McLure HA, Rubin AP. Review of local anaesthetic agents. *Minerva Anestesiol* 2005; **71**:59–74.