

PAIN

Lidocaine/tetracaine patch (Rapydan) for topical anaesthesia before arterial access: a double-blind, randomized trial

K. Ruetzler¹, B. Sima¹, L. Mayer¹, A. Golescu¹, D. Dunkler², W. Jaeger³, M. Hoefel³, J. You^{4,5}, D. I. Sessler^{5,6}, G. Grubhofer¹ and D. Hutschala^{1*}

¹ Department of Cardiothoracic and Vascular Anaesthesia and Intensive Care Medicine and ² Core Unit for Medical Statistics and Informatics, Section of Clinical Biometrics, Medical University of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria

³ Department of Clinical Pharmacy and Diagnostics, University of Vienna, Vienna, Austria

⁴ Department of Quantitative Health Sciences and ⁵ Department of Outcomes Research, Cleveland Clinic, OH, USA

⁶ Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

* Corresponding author. E-mail: doris.hutschala@meduniwien.ac.at

Editor's key points

- Pain related to cannulation can cause considerable distress and raise anxiety levels.
- Previous work has shown that a novel lidocaine/tetracaine patch can reduce venous cannulation pain.
- Here, more severe arterial cannulation pain is at least as well controlled with the new patch compared with subcutaneous lidocaine.
- The onset time is around 20 min by using heat, with less pain compared with subcutaneous injection.

Background. Arterial catheterization is painful and is associated with patient stress and anxiety. Analgesia is usually provided by subcutaneous injection of local anaesthetic. An alternative is topical anaesthesia, such as Rapydan which is a novel topical anaesthetic patch containing 70 mg each of lidocaine and tetracaine. We therefore tested the hypothesis that Rapydan patch analgesia is non-inferior to subcutaneous local anaesthetic.

Methods. Ninety patients undergoing elective major cardiac surgery were included in this prospective, double-blind clinical trial. Patients were randomly assigned to receive either a lidocaine/tetracaine patch, followed by subcutaneous injection 0.5 ml of normal saline solution, or placebo patch with subsequent subcutaneous injection of 0.5 ml of lidocaine 1%. Pain during arterial catheterization using 100-mm-long visual analogue scale (VAS) was the primary outcome. Other outcomes were pain during anaesthetic/saline injection and plasma tetracaine concentrations.

Results. VAS pain scores during arterial puncture were comparable in both groups and Rapydan was non-inferior to subcutaneous lidocaine. Pain scores at the time of subcutaneous injection were significantly lower (better) in patients assigned to the lidocaine/tetracaine patch than to lidocaine ($P=0.001$). Plasma tetracaine concentrations never exceeded the detection limit of 25 ng ml⁻¹ at any time in any patient.

Conclusions. Both the lidocaine/tetracaine patch and subcutaneous injection of lidocaine provided comparable pain control during arterial catheter insertion. Subcutaneous lidocaine caused discomfort during injection, whereas the lidocaine/tetracaine patch required placement 20 min before the procedure. Given adequate time, the patch provided better overall analgesia by obviating the need for subcutaneous infiltration.

Keywords: anaesthetics local; arteries, cannulation; drug delivery, transdermal; pain, cannulation

Accepted for publication: 2 May 2012

Many clinical procedures including arterial and venous punctures, percutaneous venous catheter insertion, lumbar puncture, and dermatological procedures are associated with pain and consequent patient discomfort.^{1,2} With the exception of venopuncture, arterial puncture is the most common invasive procedure performed on critically ill patients. Arterial catheterization is also often necessary before the induction of anaesthesia for invasive measurements of arterial pressure and collection of arterial blood samples in patients undergoing major cardiac surgery.³

Arterial puncture before induction of anaesthesia produces considerable pain. Furthermore, critical care patients describe the pain of arterial access as being worse than other types of pain.^{1,4} This procedural pain and the associated stress and anxiety are thus a substantial clinical concern.⁵ The pain of arterial puncture is usually ameliorated by injection of local anaesthetics.^{1,6,7} However, local anaesthetic injection *per se* is painful. Injection of local anaesthetics causes intradermal turgor and can trigger local vasoconstriction, both of which reduce the puncture success rate.^{2,8,9}

An alternative approach is to use topical anaesthesia for percutaneous procedures.¹⁰ However, intact skin presents a significant barrier to topical anaesthetic preparations. Therefore, topical anaesthetic preparations typically must be applied under occlusive dressings for 45–60 min before vascular access^{11 12}—which is often longer than is clinically practical.

Rapydan (also known as Synera in the USA) is a novel topical anaesthetic patch that contains 70 mg each of lidocaine and tetracaine. The central area of each Rapydan patch consists of a Controlled Heat Assisted Drug Delivery pod which is designed to warm the skin to 26–34°C, theoretically enhancing drug absorption and allowing application just 20 min before percutaneous procedures.¹³ Topical anaesthesia with a lidocaine/tetracaine patch reduces the pain of venous access.^{11 13 14} However, the efficacy of Rapydan topical analgesia has yet to be quantified for the more intense pain resulting from arterial puncture. We thus compared routine analgesia (subcutaneous injection with 0.5 ml of 1% lidocaine) with heated lidocaine/tetracaine patches. Specifically, we tested the hypothesis that lidocaine/tetracaine patch analgesia is non-inferior to that provided by subcutaneous lidocaine injection for insertion of arterial catheters.

Methods

Patients

This double-blind, randomized trial was approved by the local Ethics Committee (Medical University Vienna) and performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the European Commission. This study was registered at www.clinicaltrials.gov (identifier: NCT01494311). With written consent, 90 patients 18–90 yr old having elective valve replacement or coronary artery bypass grafting requiring arterial access before induction of

anaesthesia were included (Fig. 1). All were enrolled at the University of Vienna.

Exclusion criteria were as follows: analgesic use within 24 h before surgery, injury or infection at the planned puncture site, known allergy to local anaesthetics, drug abuse, alcoholism or psychiatric disorders, childbearing potential without adequate birth control, or an abnormal Allen's test.¹⁵

Protocol

Shortly before arterial catheter insertion, patients were randomized into one of two treatment groups (45 patients each): (i) heated lidocaine/tetracaine patch (Rapydan) and saline subcutaneous injection; or (ii) identical-appearing unheated placebo patch and subcutaneous injection of 1% lidocaine.

Randomization (1:1) was based on computer-generated codes using ARandomizer Software (<https://www.muw.ac.at/randomizer/web/login.php>) and were kept in sequentially numbered opaque envelopes that were opened just before use. An independent researcher who was not involved in data collection performed the randomization and placed an active or placebo patch on each patient's wrist in the region of maximum radial artery pulsation.

After 20 min, the patches were removed. Immediately thereafter, another investigator, blinded to the study randomization, evaluated the treatment sites for skin reactions including oedema and erythema using a five-point Likert scale (1, none; 5, vigorous). The blinded investigator then injected 0.5 ml of the study solution (saline or 1% lidocaine). Three minutes after injection, an attempt was made to cannulate the radial artery with a 20 G catheter (Becton Dickinson Critical Care System, Singapore). The investigator was permitted to give a rescue injection of lidocaine 1% (0.5 ml) if analgesia proved inadequate.

Thereafter, general anaesthesia was induced and cardiac surgery performed per our clinical routine.

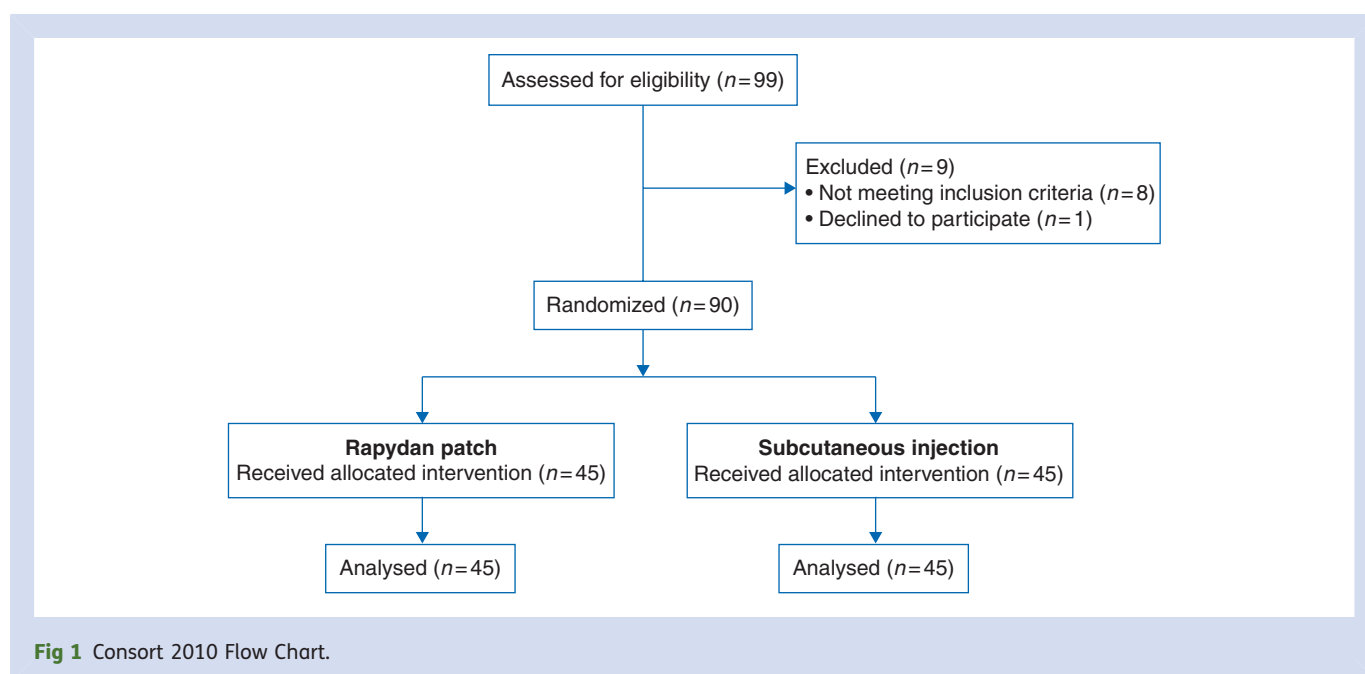


Fig 1 Consort 2010 Flow Chart.

Clinical measurements

All measurements were conducted by investigators blinded to randomization and type of cutaneous analgesia used.

After finishing the puncture procedure, patients were asked to rate their worst pain during subcutaneous injection, during insertion of the arterial cannula, and 1 min after catheter insertion using a 100-mm-long visual analogue scale (VAS).^{2, 14} The use of a VAS to measure pain and discomfort has been validated in several settings of chronic pain,^{16–18} acute postoperative pain,¹⁹ and acute non-surgical pain.²⁰

Patients also subjectively rated their procedure-related satisfaction on a four-point scale: 0, unsatisfied; 1, moderately satisfied; 2, satisfied; and 3, very satisfied.¹¹ Investigators who were unaware of the randomization estimated each patient's pain intensity at the time of catheter insertion on a four-point scale with 0 indicating no pain and 3 indicating severe pain.² The number of puncture attempts were documented and difficulty of the puncture was assessed using a five-point scale with 1 being insertion at first attempt through 5 which indicated failure to insert the catheter.

Blood for the measurement of plasma tetracaine concentrations sampled: (i) before patch application; (ii) 15 min after patch application; (iii) immediately after successful arterial puncture; (iv) 30 min after patch application; and (v) 60 min after patch application. Blood samples were kept on ice for a maximum of 30 min and were centrifuged at 4°C and 800 g for 10 min, cells were discharged, and plasma was obtained. Plasma samples and dialysate samples were frozen at –20°C and thereafter stored at –80°C until analysis. Only blood samples from patients assigned to the tetracaine/lidocaine patch were analysed.

The primary efficacy endpoint was patients' VAS scores during arterial puncture, presumably indicating the greatest pain score associated with the procedure. VAS scores during subcutaneous injection and 1 min after arterial catheter insertion served as secondary endpoints. Additional secondary endpoints included patient satisfaction, investigator's evaluation of pain during catheter insertion, difficulty of puncture, the number of puncture attempts, and the incidence of oedema and erythema at the patch site.

Determination of plasma tetracaine concentrations

The concentration of tetracaine in plasma was determined by high-performance liquid chromatography. Briefly, after the addition of 500 µl of methanol to 250 µl of plasma, the samples were centrifuged (5000g for 5 min at 4°C); 100 µl of the supernatant was injected onto the chromatography column. A Merck 'La Chrom' system (Merck, Darmstadt, Germany) was used, equipped with an L-7250 injector, an L-7100 pump, an L-7300 column oven (set at 35°C), a D-7000 interface, and an L-7400 UV detector at 290 nm.

Tetracaine was separated with a Hypersil BDS-C18 column (5 µm, 250×4.6 mm ID, Astmoor, UK) preceded by a Hypersil BDS-C18 pre-column (5 µm, 10×4.6 mm ID) at a flow rate of 1 ml min^{–1}. The mobile phase A consisted of potassium phosphate (50 mM, pH 3.0, with phosphoric acid) and

heptanesulfonic acid (5 mM) and the mobile phase B consisted of methanol. The mobile phase was filtered through a 0.45 µm filter (HVLP04700, Millipore, Vienna, Austria). The gradient ranged from 10 (0 min) to 70% at 19 and 20 min and then decreased linearly to 10% at 21 min. The columns were allowed to re-equilibrate for 14 min between runs.

Linear calibration curves were performed from the peak areas of tetracaine to the external standard by spiking drug-free human plasma with standard solutions of tetracaine hydrochloride (Sigma, Munich, Germany) at final concentrations ranging from 0.01 to 10 µl ml^{–1}. The lower limit of quantification for tetracaine in plasma was 25 ng ml^{–1}. Intra-day values for tetracaine ranged from 3.7 to 8.2% and inter-day values ranged from 4.2 to 9.5% using ranitidine in concentrations of 0.1, 0.5, 1 and 10 µg ml^{–1}.

Statistical and pharmacokinetic analyses

The lidocaine/tetracaine patch and lidocaine groups were compared for balance on patient characteristics and baseline characteristics using standard summary statistics and the standardized difference (STD) defined as the difference in means or proportions divided by the pooled standard deviation. We pre-specified a criterion of >0.30 in absolute STD as an indication of imbalance.

In our primary analysis, the lidocaine/tetracaine patch was assessed for non-inferiority to lidocaine on the VAS pain score during arterial puncture at the 0.05 significance level using a prior-specified non-inferiority delta of 10 (on the 100-mm-long scale). Non-inferiority was claimed if the upper limit of the 90% two-sided (corresponds to a 95% one-sided) confidence interval for the difference in means (lidocaine/tetracaine patch minus lidocaine) was <10. The mean difference in the VAS pain score during puncture was evaluated by analysis of covariance adjusting for the VAS pain score before puncture.

We assessed the effect of the lidocaine/tetracaine patch on pain reduction before and after arterial procedure using the Wilcoxon rank-sum test and analysis of covariance on rank data (adjusting for VAS before procedure), respectively. Also, we evaluated the effect of the lidocaine/tetracaine patch on ordinal secondary outcomes including patients' satisfaction, investigators' evaluation of pain, difficulty of arterial puncture, the number of puncture attempts, and erythema—each using a generalized estimating equation with cumulative logit link, which gives the estimated odds ratio of rating a higher ordered value. All the tests were two-tailed. A Bonferroni correction was used to adjust for multiple comparisons; $P < 0.007$ was considered statistically significant (i.e. 0.05/7).

No previous trial reports the effect of the lidocaine/tetracaine patch on the reduction in pain during arterial access. As no reliable information concerning the standard deviation of the VAS measurement was available, we used half-sampling. According to our previous experience in the operative setting with the standard practice for local anaesthesia, we assumed a standard deviation of 18 of the VAS

measurement during the puncture procedure. With 41 patients per group, we had 80% power at the 0.05 significance level to detect non-inferiority of the lidocaine/tetracaine patch on the VAS pain score during arterial puncture using a non-inferiority delta of 10 and one-sided test. Thus, a sample size of 45 patients per group allowing for 10% dropout was selected to ensure an adequately powered study.

SAS software version 9.3 for Windows (SAS Institute, Cary, NC, USA) was used for analyses.

Results

A total of 90 patients (45 patients in each group) were enrolled between March and June 2011. All patients were included in the analysis. Baseline characteristics were well balanced between the two randomized groups (absolute STD <0.30; Table 1).

The VAS pain score during arterial puncture was 26 (16) mm in the lidocaine/tetracaine patch group and 29 (22) mm in the lidocaine group, respectively (Fig. 2), with a mean difference of {0.3 [90% confidence interval (CI): -6.9, 7.5], lidocaine/tetracaine patch - lidocaine} after adjusting for the VAS score before puncture. The lidocaine/tetracaine patch was non-inferior to lidocaine on the VAS pain score during puncture, since the upper limit of the confidence interval for the mean difference (7.5) was below the non-inferior criterion of 10.

Results of secondary outcomes are summarized in Table 2. The VAS score at the time of subcutaneous injection was significantly lower (better) in the tetracaine/lidocaine patch group [median (Q1, Q3): 0 (0, 0)] than in the lidocaine group [4 (0, 20), $P=0.001$]. However, no significant difference was observed in the VAS score after arterial puncture [lidocaine/tetracaine patch: 0 (0, 5) vs lidocaine: 0 (0, 0); $P=0.04$, after adjusting for the VAS before puncture].

Neither the patients' pain evaluation ($P=0.07$) nor the investigators' pain evaluation ($P=0.02$) differed significantly in the two randomized groups. The corresponding odds ratios (99.3% CI) of selecting a higher ordered value in patient's evaluation (more satisfied) and in investigator's evaluation (more severe pain) were 1.70 (0.77, 3.75) and

0.57 (0.29, 1.11) (lidocaine/tetracaine patch vs lidocaine), respectively. Furthermore, no group differences were found in any other secondary outcomes, including puncture difficulty ($P=0.94$), puncture attempts ($P=0.93$), or erythema ($P=0.80$).

Plasma tetracaine concentrations never exceeded the detection limit of 25 ng ml⁻¹ at any time in any patient. No adverse events or clinical complications related to the tetracaine/lidocaine or placebo patches were observed. Oedema was never observed in either group. In three patients (6.7%) in the tetracaine/lidocaine patch group and two patients (4.4%) in the lidocaine group, mild-to-moderate erythema at the puncture site was observed.

Discussion

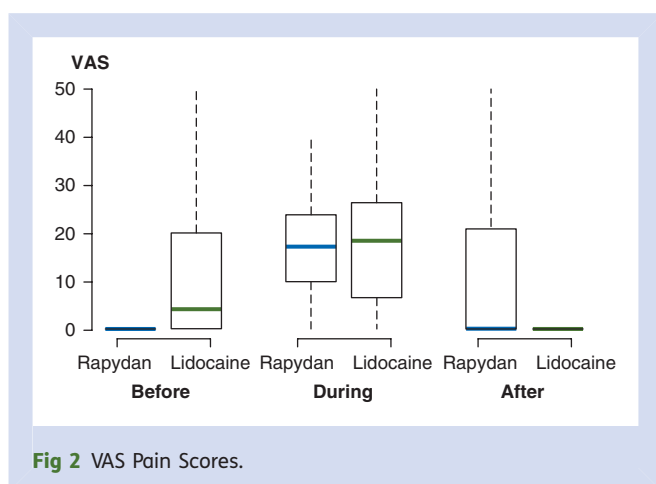
Topical anaesthesia with the lidocaine/tetracaine patch has been shown to reduce the pain of venopuncture.^{2 12} However, arterial catheter insertion is considerably more painful, and thus associated with greater patient stress and anxiety. Subcutaneous infiltration of local anaesthetic remains the most common analgesic approach. One result of our study, though, is that injection of local anaesthetic *per se* causes considerable pain.

Topical analgesia is an attractive alternative to subcutaneous infiltration which itself is painful.¹² However, intact skin presents a significant barrier to topical anaesthetic absorption. The current topical anaesthetic preparations must therefore be applied at least 45 min before vascular access to provide adequate analgesia.²¹ For example, the recommended application time for EMLA, a widely used eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, is 60 min.²¹

The lidocaine/tetracaine patch differs from previous formulations both in the anaesthetic mixture and—more importantly—in being actively heated. Topical heating increases regional blood flow which presumably enhances local transcutaneous absorption of the local anaesthetic. Consistent with this theory, the tetracaine/lidocaine patch and subcutaneous lidocaine infiltration provided comparable analgesia for arterial catheter insertion. Our results are also consistent with those of Curry and Finkel¹³ who reported

Table 1 Patient characteristic and baseline characteristics (n=90). Summary statistics are percentage of patients or median [Q1, Q3] (min, max). *STD, standardized differences (Rapydan-lidocaine): difference in means or proportions divided by pooled standard deviation; >0.3 in absolute value indicates imbalance. CABG, coronary arterial bypass graft

	Lidocaine/tetracaine patch (n=45)	Lidocaine (n=45)	STD
Age (yr)	68 [54, 75] (28, 86)	69 [59, 74] (29, 84)	-0.10
Gender (female) [no. (%)]	8 (18)	12 (27)	-0.21
Body mass index (kg m ⁻²)	27 [25, 30] (21, 45)	27 [24, 30] (20, 38)	0.09
ASA status (III vs II) [no. (%)]	45 (100)	44 (98)	0.21
Type of surgery [no. (%)]			
CABG	17 (38)	18 (40)	0.19
Valve	20 (44)	22 (49)	
CABG + valve	8 (18)	5 (11)	



sufficient analgesia for peripheral venous access after a 20 min patch application. A reduction in application time from 45 min or more to just 20 min is substantial and likely to enhance the product's clinical utility.

Several clinical studies reported mild side-effects in the use of the lidocaine/tetracaine patch including mild erythema, oedema, blanching, and burning sensations.^{22 23} However, the only cutaneous complication we observed with mild erythema and the incidence was comparable in the lidocaine/tetracaine patch and placebo groups. However, our study is far too small to evaluate any but the most common complications. Additional clinical experience will thus be necessary to confirm that the system is safe.

A rare, but serious complication in the use of anaesthetic patches, such as EMLA, is the systemic adsorption of anaesthetic agents including prilocaine which can cause

Table 2 Effect of lidocaine/tetracaine patch (Rapydan) on secondary outcomes (n=90). *The confidence intervals and the P-values were adjusted for multiple comparisons by the Bonferroni correction. The significance criterion was 0.007 (i.e. 0.05/7). †Proportional odds logistic regression, unless specified. ‡Wilcoxon's rank-sum test. §Statistically significant. ¶Analysis of covariance on ranks adjusting for the VAS score before arterial puncture. ||Odds ratio of rating a lower ordered value for the Rapydan group vs the lidocaine group. #1 being insertion at first attempt through 5 which indicated failure to insert the catheter

	Rapydan (n=45)	Lidocaine (n=45)	Treatment effect (99.3% CI)* (Rapydan vs lidocaine)	P-value*†
VAS (100 mm scale)			Median difference	
During injection	0 (0, 0)	4 (0, 20)	0 (−7, 0)	0.001‡,¶
After arterial puncture	0 (0, 5)	0 (0, 0)	0 (0, 0)	0.04§
Patient satisfaction, no.			Odds ratio	
1—moderately satisfied	0	4	1.7 (0.8, 3.8)	0.07
2—satisfied	8	10		
3—very satisfied	37	31		
Investigator evaluation, no.			0.6 (0.3, 1.1)	0.02
0—no pain	26	17		
1—mild pain	15	17		
2—moderate pain	4	10		
3—severe pain	0	1		
Puncture difficulty, # no.			1.0 (0.5, 2.0)	0.94
1	25	26		
2	14	13		
3	4	4		
4	2	1		
5—most difficult	0	1		
Attempts, no.			1.0 (0.5, 2.2)	0.93
1	33	34		
2	9	8		
3	3	2		
4	0	1		
Oedema (none), no.	45	45	—	>0.99
Erythema, no.			1.1 (0.3, 3.7)	0.80
1—none	42	43		
2—mild	3	1		
3—moderate	0	1		

methemoglobinaemia.²¹ The tetracaine/lidocaine patch consists of lidocaine and tetracaine, 70 mg each. Even rapid i.v. injection of 70 mg of lidocaine would not cause systemic toxicity or increase plasma lidocaine to concentrations near 1 $\mu\text{g ml}^{-1}$ that are associated with agitation, central nervous system depression, or both.¹⁰ Systemic absorption of tetracaine thus seems to be the only potential systemic toxicity that might be expected from patch use.

Tetracaine plasma concentrations never even exceed the 25 ng ml^{-1} detection threshold in our patients and thus remained well below the toxic threshold which is $\sim 200 \text{ ng ml}^{-1}$.²⁴ Our results are consistent with several studies in adults and children which revealed that the plasma concentrations of lidocaine and tetracaine were well below the toxic levels; furthermore, no systemic toxic effects have been reported from the use of lidocaine/tetracaine patches.¹⁰ Our results, combined with previous reports, strongly suggest that the appropriate use of heated lidocaine/tetracaine patches is extremely unlikely to provoke systemic toxicity.

The design of this study attempted to ensure that the investigator and patients remained blinded to randomization. One aspect of the tetracaine/lidocaine patch—the associated heat—may have led to partial unblinding of the patients, although they were not told to expect local warming. Subject-reported visual analogue pain scores were in fact similar in patients with active patches and subcutaneous lidocaine, suggesting no bias towards the novel treatment.

In summary, both the tetracaine/lidocaine patch (Rapydan) and subcutaneous injection of lidocaine provided comparable pain control during arterial catheter insertion. Subcutaneous lidocaine caused discomfort during injection, whereas the tetracaine/lidocaine patch requires placement 20 min before the procedure. Given adequate time, the patch provides better overall analgesia by obviating the need for subcutaneous infiltration.

Declaration of interest

None declared.

Funding

Financially supported by Torrex Chiesi Pharma (Vienna, Austria). The study was designed by the investigators alone. The sponsor was not involved in study design, data collection, analysis, or interpretation of the data; the manuscript was written by the investigators. None of the other authors has a personal financial interest related to this research.

References

- Hudson TL, Dukes SF, Reilly K. Use of local anesthesia for arterial punctures. *Am J Crit Care* 2006; **15**: 595–9
- Sawyer J, Febbraro S, Masud S, Ashburn MA, Campbell JC. Heated lidocaine/tetracaine patch (Synera, Rapydan) compared with lidocaine/prilocaine cream (EMLA) for topical anaesthesia before vascular access. *Br J Anaesth* 2009; **102**: 210–15
- Schlack WS, Boermeester MA. Patient safety during anaesthesia: incorporation of the WHO safe surgery guidelines into clinical practice. *Curr Opin Anaesthesiol* 2010; **23**: 754–8
- Hamm JB, Nguyen BV, Kiss G, et al. Assessment of a cardiac output device using arterial pulse waveform analysis, Vigileo, in cardiac surgery compared to pulmonary arterial thermodilution. *Anaesth Intensive Care* 2010; **38**: 295–301
- Eidelman A, Weiss JM, Lau J, Carr DB. Topical anesthetics for dermal instrumentation: a systematic review of randomized, controlled trials. *Ann Emerg Med* 2005; **46**: 343–51
- Eichenfield LF, Funk A, Fallon-Friedlander S, Cunningham BB. A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children. *Pediatrics* 2002; **109**: 1093–9
- Masud S, Wasnich RD, Ruckle JL, et al. Contribution of a heating element to topical anesthesia patch efficacy prior to vascular access: results from two randomized, double-blind studies. *J Pain Symptom Manage* 2010; **40**: 510–19
- Arildsson M, Nilsson GE, Stromberg T. Effects on skin blood flow by provocation during local analgesia. *Microvasc Res* 2000; **59**: 122–30
- Arildsson M, Asker CL, Salerud EG, Stromberg T. Skin capillary appearance and skin microvascular perfusion due to topical application of analgesia cream. *Microvasc Res* 2000; **59**: 14–23
- Tadicherla S, Berman B. Percutaneous dermal drug delivery for local pain control. *Ther Clin Risk Manag* 2006; **2**: 99–113
- Batoz H, Verdonck O, Pellerin C, Roux G, Maurette P. The analgesic properties of scalp infiltrations with ropivacaine after intracranial tumoral resection. *Anesth Analg* 2009; **109**: 240–4
- Wiles MD, Dobson SA, Moppett IK. The effect of a new topical local anaesthetic delivery system on forearm skin blood flow reactivity. *Anaesthesia* 2010; **65**: 178–83
- Curry SE, Finkel JC. Use of the Synera patch for local anesthesia before vascular access procedures: a randomized, double-blind, placebo-controlled study. *Pain Med* 2007; **8**: 497–502
- Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of visual analog scales for measurement of pain. *Clin Pharmacol Ther* 1983; **34**: 234–9
- Kohonen M, Teerenhovi O, Terho T, Laurikka J, Tarkka M. Is the Allen test reliable enough? *Eur J Cardiothorac Surg* 2007; **32**: 902–5
- Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976; **2**: 175–84
- Gaston-Johansson F, Gustafsson M. Rheumatoid arthritis: determination of pain characteristics and comparison of RAI and VAS in its measurement. *Pain* 1990; **41**: 35–40
- Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain* 1993; **55**: 195–203
- DeLoach LJ, Higgins MS, Caplan AB, Stiff JL. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg* 1998; **86**: 102–6
- Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; **113**: 9–19
- Tahir A, Webb JB, Allen G, Nancarrow JD. The effect of local anaesthetic cream (EMLA) applied with an occlusive dressing on skin thickness. Does it matter? *J Plast Reconstr Aesthet Surg* 2006; **59**: 404–8

- 22 Sethna NF, Verghese ST, Hannallah RS, Solodiuk JC, Zurakowski D, Berde CB. A randomized controlled trial to evaluate S-Caine patch for reducing pain associated with vascular access in children. *Anesthesiology* 2005; **102**: 403–8
- 23 Berman B, Flores J, Pariser D, Pariser R, de Araujo T, Ramirez CC. Self-warming lidocaine/tetracaine patch effectively and safely induces local anesthesia during minor dermatologic procedures. *Dermatol Surg* 2005; **31**: 135–8
- 24 Murtaza R, Jackman HL, Alexander B, Lleshi-Tali A, Winnie AP, Igic R. Simultaneous determination of mepivacaine, tetracaine, and *p*-butylaminobenzoic acid by high-performance liquid chromatography. *J Pharmacol Toxicol Methods* 2001; **46**: 131–6