J Anesth (2012) 26:552–555
DOI 10.1007/s00540-012-1360-3

ORIGINAL ARTICLE

Availability of a 5% lidocaine patch used prophylactically for venipuncture- or injection-related pain in children

Cheul-Hong Kim · Ji-Uk Yoon · Hyeon-Jung Lee · Sang-Wook Shin · Ji-Young Yoon · Gyeong-Jo Byeon

Received: 26 April 2011 / Accepted: 12 February 2012 / Published online: 9 March 2012

Abstract
Purpose Venipuncture- or injection-related pain is still major problem during anesthetic induction in children. This study was designed to determine the availability of a 5% lidocaine patch used prophylactically for venipuncture- or injection-related pain during the induction of anesthesia.
Methods In a randomized, double-blind study, 72 pediatric patients were allocated to one of two groups: pretreatment with a 5% lidocaine patch (Lidoderm®, Endo Pharmaceuticals, Chadds Ford, PA, USA) (group A) or pretreatment with a placebo patch (group B). Pain severity was evaluated on the Faces, Legs, Activity, Cry, and Consolability Scale (FLACC) during venipuncture, and a 4-point scale during the injection of rocuronium.
Results The FLACC score during venipuncture was significantly lower for group A than group B ($p < 0.001$). There was no significant difference in the grades of the 4-point scale observed during the injection of rocuronium between groups A and B. No significant adverse effect was noted for the groups.
Conclusion Although pretreatment with a 5% lidocaine patch was found to be a safe, effective, and simple method of preventing venipuncture pain in children, this method did not reduce drug injection pain during the induction of anesthesia.

C.-H. Kim
Department of Anesthesia and Pain Medicine, School of Dentistry, Pusan National University, Gyeongnam, Korea

J.-U. Yoon (✉) · H.-J. Lee · S.-W. Shin · J.-Y. Yoon · G.-J. Byeon
Department of Anesthesia and Pain Medicine, School of Medicine, Pusan National University, Mulgeum-eup, Yangsan-si, Gyeongnam 626-770, Korea
e-mail: nuncoip@hanmail.net

Keywords Anesthetics · Local · Lidocaine · Rocuronium · Transdermal administration

Introduction

Children express considerable fear, agitation, and distress during hospital procedures that involve needles [1]. The procedural pain and associated stress and anxiety involved for pediatric patients represent a significant clinical concern. Furthermore, it is also known that movements in the arm associated with the injection of rocuronium after the induction of anesthesia are associated with pain [2]. The incidence and severity of withdrawal movement during the injection of rocuronium is estimated to be higher in pediatric than in adult patients.

Although most topical formulations such as 5% lidocaine–prilocaine cream and 4% tetracaine gel provide adequate cutaneous analgesia for a variety of clinical situations during venipuncture, there have been limitations to most of these formulations and reports of adverse reactions [3, 4]. Among the opioids, only remifentanil has been tried and shown to be effective at reducing rocuronium-induced movement in children in recent clinical research [5]. The Lidoderm Patch (Lidoderm®, Endo Pharmaceuticals, Chadds Ford, PA, USA) is a noninvasive drug delivery system that delivers 5% lidocaine. The depth of the anesthetic effect depends mainly on the duration of application. When applied for 60 min, the depth of the anesthetic effect was found to be 3 mm, and for 120 min of application time, the depth of the anesthetic effect was found to be 5 mm [6, 7]. Although several studies have suggested that the 5% lidocaine patch could prove useful for neuropathic and nonneuropathic pain conditions, an analgesic effect on rocuronium-induced pain is yet to be demonstrated [8, 9].

We postulated that pretreatment with the 5% lidocaine patch would reduce both venipuncture pain and rocuronium-induced pain. Thus, the purpose of the present study was to examine the analgesic effect of the 5% lidocaine patch compared with a placebo patch alone during venipuncture and rocuronium injection in children.

Materials and methods

Formulations

The 5% lidocaine patch (Lidoderm®) contains 700 mg of lidocaine in an aqueous base. The size of the patch is 10 cm × 14 cm. The lidocaine patch was activated and administered by removing the patch from its airtight pouch, peeling the release liner, and applying the patch to the skin on the wrist with a tape for a surgical drape (Ioban™ 2, 3M Healthcare, Neuss, Germany).

For the placebo patch, we did not remove the release liner, and we applied the patch to the skin on the wrist with a surgical drape. Thus, the active patch and the placebo patch were identical in weight, shape, and color.

Study design and patient selection

This was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of a 5% lidocaine patch in preventing venipuncture pain as well as rocuronium-induced pain in children. This study was approved by the Institutional Review Boards and conducted according to the Declaration of Helsinki. Informed consent was obtained from a parent for the pediatric patients prior to their participation in the study.

Seventy-two ASA physical status I patients aged 4–15 years presenting for elective surgery were allocated (by sealed envelopes including computer-generated random numbers) into two groups: pretreatment with a 5% lidocaine patch (Lidoderm®) (group A) or pretreatment with a placebo patch (group B).

Exclusion criteria consisted of (1) known sensitivity to any of the active or inactive ingredients in the active or placebo patch; (2) damaged, denuded, or broken skin at the designated patch site; or (3) the use of prescription-strength analgesic medication during the 24 h period prior to the procedure.

After cleansing with an alcohol sponge, the patch was applied over a wide area (10 cm × 14 cm width) of the nondominant hand and distal forearm 120 min before surgery following allocation to the groups. During patch application, the investigator evaluated the treatment area for erythema, edema, or adverse skin reactions.

On arrival in the operating room, the patients were monitored with electrocardiography, pulse oximetry, and noninvasive measurement of blood pressure. The patch was removed after an anesthetic nurse had marked the margin of the area to which the patch was attached. The anesthesiologists who performed venipuncture did not know whether a 5% lidocaine patch or a placebo patch had been used. A 24-gauge cannula was inserted into a suitable vein on the dorsum of the nondominant hand so that the entry points of the catheter were within the marked area and the final positions of the tip were at the center of the marked area. The anesthesiologist evaluated pain severity using the Faces, Legs, Activity, Cry, and Consolability Scale (FLACC) during venipuncture [10]. While providing 100% O_2 via a facial mask, 2.5% thiopental 5 mg/kg was injected over 30 s. After loss of consciousness (confirmed by loss of ciliary reflex), rocuronium 0.6 mg/kg without dilution (10 mg/ml) was injected over 10 s. During the study period, the flow of the i.v. fluid was maintained at a rate of 5–7 ml/min. Assisted ventilation with 100% oxygen was commenced at an appropriate time. An investigator who was unaware of the patient group assignments observed the movements of the patients during and immediately after rocuronium administration. The patient response was graded on a 4-point scale: 1, no response; 2, movement at the wrist only; 3, movement involving the arm only (elbow or shoulder); 4, movement in more than one extremity or generalized response. A grade of 2 or more was regarded as movement.

Statistical analysis

All statistical analysis was performed using Statview 5.0 (SAS Institute, Cary, NC, USA) and MedCalc ver. 11.2 (MedCalc Software, Mariakerke, Belgium). Nonparametric tests were used as the data were not considered to be normally distributed. The Mann–Whitney *U* test was used to determine differences between groups A and B in the FLACC scores. Data are presented as the median (25th–75th percentile). Four-point scale grades were analyzed with the chi-square test, and data are presented as absolute frequencies (*n*) for frequency data. *P* values <0.05 were deemed statistically significant.

Results

Seventy-seven pediatric patients were randomly allocated to two groups. Two patients in group A and 3 patients in group B were excluded because of inappropriate application of the active or placebo patch or failure of intravenous cannulation. Thus, 72 patients were analyzed. Demographic data were comparable between groups A and B (Table 1). Duration of surgery, duration of anesthesia, and time to recovery were also comparable.

Table 1 Demographic data

	Group A ($N = 40$)	Group B ($N = 32$)	p value
Age (years)	8.9 ± 2.7	9.4 ± 5.4	0.636
Sex (M/F)	23/17	17/15	0.382
Weight (kg)	33.3 ± 10.8	30.7 ± 9.9	0.425

Values are expressed as mean ± SD or number

Group A pretreatment with a 5% lidocaine patch, *Group B* pretreatment with a placebo patch

Table 2 FLACC scores during venipuncture

	Group A ($N = 40$)	Group B ($N = 32$)	p value
FLACC	0 (0–1)	4 (1–7)	<0.001

Values are expressed as median (25th–75th percentile)

Group A pretreatment with a 5% lidocaine patch, *Group B* pretreatment with a placebo patch

Table 3 Four-point scale of rocuronium response

	Group A ($N = 40$)	Group B ($N = 32$)	p value
Grade			0.917
1	3 (7.5%)	5 (15.6%)	
2	6 (15%)	3 (9.4%)	
3	13 (32.5%)	7 (21.9%)	
4	18 (45%)	17 (53.1%)	
Total (2, 3, 4)	37 (92.5%)	27 (84.4%)	

Values are expressed as number (%)

Group A pretreatment with 5% lidocaine patch, *Group B* pretreatment with placebo patch

The FLACC scores during venipuncture were also significantly reduced after pretreatment with the 5% lidocaine patch in group A compared with group B ($p < 0.001$; Table 2). The incidence of overall withdrawal movement on injection of rocuronium was 92.5% (37/40) in group A and 84.4% (27/32) in group B. The incidence of generalized movement (grade 4) was 45% (18/40) in group A and 53.1% (17/32) in group B. There were no significant differences in the withdrawal movement grade between groups A and B (Table 3).

Discussion

Our results indicated that pretreatment with the 5% lidocaine patch was effective at reducing pain during venipuncture, whereas it did not reduce rocuronium injection pain in children.

Pain severity was evaluated on the FLACC scale during venipuncture, and the 4-point scale during injection of rocuronium. The Faces, Legs, Activity, Cry, and Consolability (FLACC) pain scale is an observational pain scale consisting of 5 behavioral components that provide a global pain score ranging from 0 to 10 [10]. FLACC was recommended by von Baeyer and Spagrud [11] for the assessment of procedural pain in children aged 3–18 years.

The underlying mechanisms for rocuronium-induced pain are still not fully understood. Rocuronium is supplied in a sterile, nonpyrogenic, isotonic solution. Isotonicity is obtained with sodium chloride and a pH of 4 by adding acetic acid or sodium hydroxide. The relatively low pH of the rocuronium solution may be a possible cause, as Klement and Arndt [12] have shown that injecting acid solutions with a pH of 4 or less causes pain on injection, which increases linearly with decreasing pH. It is well known that tissue acidosis induces pain. For example, direct application of an acidic solution into the skin produces nonadapting pain. Acid-sensing ion channels (ASICs), proton-gated cation channels that belong to the epithelial sodium channel/degenerin superfamily, could be associated with this pain. Activation of ASICs by protons results in sodium and calcium influxes [13]. Lin et al. [14] reported that ASIC currents are significantly inhibited by lidocaine in cultured mouse cortical neurons. Other mediators such as a kininogen cascade may be involved; this was postulated to explain the pain associated with propofol injection [15]. The pain associated with propofol and rocuronium is similar: it appears immediately during administration, duration is short, and intensity decreases with subsequent injection.

McCluskey et al. [16] reported that topical anesthesia with EMLA cream applied for 60 min does not reduce propofol-induced pain, and the patients treated with EMLA cream had a higher incidence (76%) of propofol-induced pain compared to the lidocaine group (37%), although the EMLA cream alleviated the incidence of venipuncture pain to some degree (83% in the untreated group vs. 50% in the group treated with EMLA). Similarly, our results showed that the 5% lidocaine patch reduced venipuncture pain to a median FLACC score of 0 (compared to 4 in group B), but the 5% lidocaine patch did not reduce rocuronium-induced pain.

The depth of the anesthetic effect depends mainly on the duration of application. When applied for 60 min, the depth of the anesthetic effect was found to be 3 mm, and for 120 min of application time, the depth of the anesthetic effect was found to be 5 mm [6, 7]. Another investigator demonstrated that applying a topical anesthetic for more than 120 min could be acceptable for venous cannulation; lidocaine penetrates to depths of >3 mm after 120 min [6]. Thus, we allowed 120 min of application time in this study. Nevertheless, applying the 5% lidocaine patch for 120 min was not enough to reduce rocuronium-induced pain.

It has been reported that the systemic absorption rate of lidocaine from a 5% lidocaine patch applied to the skin in humans is very low. The maximum plasma lidocaine concentration was approximately 0.186 μg/ml after 4 lidocaine patches were applied for 24 h, which is approximately 12–15% of the lidocaine concentration associated with cardiac activity and 4–5% of that associated with systemic toxicity [17]. Thus, the 5% lidocaine patch provides a treatment option that carries a low systemic adverse event and drug–drug interaction risk burden, even with the continuous application of up to 4 patches per day.

In Korea, a 5% lidocaine patch (US $1.38) is more expensive than 2% lidocaine (US $0.35 for 1 vial). This may delay the widespread use of the lidocaine patch as a prophylactic for venipuncture pain. Thus, we studied the effect of the 5% lidocaine patch on rocuronium-induced pain. However, we found that the 5% lidocaine patch did not decrease rocuronium-induced pain.

These results show that venous cannulation pain is different from rocuronium-induced pain in depth and mechanism.

In conclusion, pretreatment with a 5% lidocaine patch before anesthesia could be a novel, simple, and acceptable prophylactic for venipuncture pain in children, but is not an adequate pretreatment for rocuronium-injection pain.

References

1. Cummings EA, Reid GJ, Finley GA, McGrath PJ, Ritchie JA. Prevalence and source of pain in pediatric inpatients. Pain. 1996;68:25–31.
2. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? Br J Anaesth. 1997;79:382–3.
3. 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.
4. Kleiber C, Sorenson M, Whiteside K, Gronstal BA, Tannous R. Topical anesthetics for intravenous insertion in children: a randomized equivalency study. Pediatrics. 2002;110:758–61.
5. Kim JY, Kim JY, Kim YB, Kwak HJ. Pretreatment with remifentanil to prevent withdrawal after rocuronium in children. Br J Anaesth. 2007;98:120–3.
6. Bjerring P, Arendt-Nielsen L. Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream. Br J Anaesth. 1990;64:173–7.
7. Wahlgren CF, Quiding H. Depth of cutaneous analgesia after application of a eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA cream). J Am Acad Dermatol. 2000; 42:584–8.
8. Hines R, Keaney D, Moskowitz MH, Prakken S. Use of lidocaine patch 5% for chronic low back pain: a report of four cases. Pain Med. 2002;3:361–5.
9. Katz NP, Gammaitoni AR, Davis MW, Dworkin RH, Lidoderm Patch Study Group. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. Pain Med. 2002;3:324–32.
10. Crellin D, Sullivan TP, Babl FE, O'Sullivan R, Hutchinson A. Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting. Paediatr Anaesth. 2007; 17:720–33.
11. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. Pain. 2007;127:140–50.
12. Klement W, Arndt JO. Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. Br J Anaesth. 1991;66:189–95.
13. Deval E, Gasull X, Noel J, Salinas M, Baron A, Diochot S, Lingueglia E. Acid-sensing ion channels (ASICs): pharmacology and implication in pain. Pharmacol Ther. 2010;128:549–58.
14. Lin J, Chu X, Maysami S, Li M, Si H, Cottrell JE, Simon RP, Xiong Z. Inhibition of acid sensing ion channel currents by lidocaine in cultured mouse cortical neurons. Anesth Analg. 2011;112:977–81.
15. Scott RP, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection. Anaesthesia. 1988;43:492–4.
16. McCluskey A, Currer BA, Sayeed I. The efficacy of 5% lidocaine–prilocaine (EMLA) cream on pain during intravenous injection of propofol. Anesth Analg. 2003;97:713–4.
17. Gammaitoni AR, Alvarez NA, Galer BS. Pharmacokinetics and safety of continuously applied lidocaine patches 5%. Am J Health Syst Pharm. 2002;59:2215–20.