The use of the S-Caine patch is safe and feasible in children younger than three

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ABSTRACT

Background: Topical S-Caine patches with a eutectic 70mg lidocaine/70mg tetracaine mixture and air-activated heating element are safe and efficient for local intact skin anaesthesia before painful punctures in children older than three. This study is the first to evaluate its safety and feasibility of use in children younger than three years.

Methods: In this prospective interventional single-dose pharmacokinetic study, children under three admitted with central catheters were eligible for inclusion. Following a 30-minute skin application of a single S-Caine Patch, lidocaine plasma concentrations were measured over a 4-hour period using a validated Liquid Chromatography with Photodiode Array detection method. Maximum plasma concentrations (Cmax) were compared to a predefined safety threshold of 0.100 mg/L, corresponding to one-tenth of the lowest concentration associated with potential clinical effects. Both local and systemic adverse events were monitored and analysed for incidence and severity. Caregiver satisfaction was assessed using Likert scales, with scores ≥ 4 out of 5 indicating "excellent" feasibility. Subgroup analysis was performed after stratifying for demographic (age, sex, ethnicity, weight-for-height ratio) and procedural variables (vascular access type and patch application site).

Results: Sixty-seven patients (median 0.55 [0.13 – 1.09] years, range 3 days to 3 years, 58.2% male) were included. **Safety**: Median lidocaine plasma concentrations at -15, 15, 30, 60, 120, and 240 min post-application and maximum concentration (Cmax) were 0.005 [0.005–0.005] mg/L, 0.005 [0.005–0.005] mg/L, 0.018 [0.005–0.036] mg/L, 0.020 [0.005–0.031] mg/L, 0.016 [0.005–0.029] mg/L, 0.013 [0.005–0.026] mg/L, and 0.025 [0.014–0.038] mg/L, respectively. Concentrations at all time points and Cmax remained significantly below the safety threshold, and this was valid across all demographic and procedural subgroups ($p<0.001$). Only 2 patients exceeded the safety threshold (Cmax 0.270 and 0.110 mg/L at 15 and 30min post-application, respectively) without any clinical repercussions. **Adverse events** occurred in 49 patients (73.1%), manifesting exclusively as transient local erythema. Two cases (4.1%) were rated as more than moderate in severity. All adverse events resolved spontaneously within 30 minutes after patch removal, except for 7 patients in whom symptoms persisted longer but did decrease in intensity. **Feasibility**: Overall satisfaction was reported as "excellent" in 58 patients (86.6%) regarding patch application and 55 (82.1%) at patch removal, with mean Likert scores of 4.5/5 and

4.4/5, respectively. Adverse event occurrence and feasibility ratings were independent of demographic or procedural characteristics.

Conclusion: The use of S-Caine Patch in children younger than three is safe, as plasma lidocaine concentrations remain far below the safety threshold, and only transient minor local adverse events are seen. Feasibility is scored positively.

Keywords: Paediatrics; Infant; Pain Management; Anaesthetics, Local; Lidocaine; Pharmacokinetics; Safety; Feasibility

INTRODUCTION

When children become patients, they frequently undergo painful procedures such as cannulation, blood sampling, and other punctures through sensitive skin (1,2). These are more distressing in young children than in adults, especially in the emergency department (ED) or paediatric intensive care unit (PICU) where mechanically ventilated patients undergo more painful procedures (3). Clinicians still underestimate pain, though adequate pain management is essential (1,4,5). Ignoring pain perception leads to negative short- and long-term effects on the child's clinical outcomes, development and behaviour (e.g., heightened physiological pain responses and pain sensitivity, poorer recovery, increased pain and anxiety surrounding future medical procedures)(6,7). Over the past decades, improved recognition has led to better use of both pharmacologic and nonpharmacologic strategies (8).

There are numerous topical anaesthetics available, including liposomal lidocaine or tetracaine, or a lidocaine/prilocaine eutectic mixture - one with a melting point lower than that of its individual components -, which provide as non-invasive alternatives to injectable anaesthesia (9). Despite their widespread use, these agents have limitations such as delayed onset, limited absorption, and local side effects (10–12). These challenges are particularly relevant in infants and toddlers, where pharmacokinetic data are scarce making effective pain management a persistent clinical challenge. In this age group, the most frequently used agents are lidocaine/prilocaine cream (EMLA® 5%) and tetracaine gel (amethocaine 4%, Ametop®). However, multiple trials and meta-analyses have shown mixed results regarding their relative advantages in terms of analgesic efficacy, application time, and cost, making it difficult to determine a clearly superior option (4,9,13–15). The ideal topical anaesthetic would therefore combine safety, rapid onset, prolonged duration, and ease of application (1).

The lidocaine/tetracaine patch (Synera®/Rapydan®), contains 70 mg of each agent, and uses Controlled Heat-Assisted Drug Delivery (CHADD) technology to warm the skin to 39–41 °C, enhancing dermal absorption and promoting vasodilation (9,10,16–20). Compared to EMLA®, the patch demonstrates a faster onset of action (≤ 30 minutes), a longer duration of effect (≤ 120 minutes), and a deeper level of anaesthesia (up to 6.8 mm)(9,11,21–23). Moreover, it significantly reduces pain compared to placebo (e.g., 59% vs. 20%)(24) and outperforms EMLA® in both pain incidence (12% vs. 46%)(25) and first-

attempt cannulation success (92.4% vs. 85%)(26), supporting its efficacy as a topical anaesthetic in children older than three.

Assessing safety requires understanding the pharmacokinetics and toxicity of lidocaine and tetracaine. Absorption depends on dose, skin integrity, and application time; in older children, up to two 30-minute applications within 24 hours are recommended (27). In children over three years, pharmacokinetic data show rapid systemic absorption during the first two hours, with substantially higher plasma concentrations from heated versus unheated patches, but no significant increase in systemic exposure or altered elimination kinetics with use beyond four hours (17). Lidocaine undergoes primary hepatic metabolism to active compounds such as monoethylglycinexylidide (MEGX), which can contribute to systemic toxicity (11,27,28). Its elimination half-life averages 1.8 hours in children but may extend to 12 hours with transdermal use or hepatic impairment (29), while renal clearance - reduced in infants - plays a key role in its excretion (27). Toxic effects - such as central nervous system symptoms, cardiac depression, and arrhythmias - typically occur at serum levels above 5 mg/L in adults. CNS toxicity and seizures might - according to one author – occur in infants at levels as low as 1 mg/L, due to immature metabolism, reduced protein binding, and a higher surface-to-weight ratio (28–30), although no case was reported. While a single S-Caine patch is unlikely to cause systemic toxicity, applying multiple patches concurrently or consecutively may increase plasma levels and the risk of systemic effects (32).

Data on tetracaine are more limited, due to its rapid hydrolysis and instability (26,33). While systemic toxicity is rare, isolated cases - such as in a premature neonate - have been reported (34). No consistent systemic toxicity has been observed in children older than three (18,28,35,36).

Objective

Due to the lack of data and studies, the use of the S-Caine patch in children under three years old is currently not recommended. This study aims to evaluate safety and feasibility of the S-Caine patch in this age group.

METHODS

Study population

This prospective, single-arm, interventional pharmacokinetic study was conducted from October 2019 to November 2024 at the Department of Paediatrics and PICU of UZ Brussel, Belgium. Hospitalised children under three years of age, with stable vital signs, and in whom a central catheter was placed as part of standard clinical care, were eligible for inclusion. The list of exclusion criteria can be found in ***Table S1.*** After completing the checklist of inclusion/exclusion criteria and obtaining written informed consent, a S-Caine Patch was applied for 30 minutes to intact skin. Localisations of the patch application on the skin corresponded to the places where punctures would normally be performed, excluding the nappy area due to concerns about excessive parabens penetrations because of skin immaturity (37). A registration form was completed per patient, and all patient and outcome data were collected and stored in REDCap version 13.3.5 (Vanderbilt University, Nashville, TN, USA).

Safety

Lidocaine plasma concentrations were measured at six different time points via central catheters. The first blood sample was obtained not more than 15 minutes before the application of the patch (t_{-15}). The remaining five plasma samples were collected at 15 minutes (t_{15}), and 30 minutes (t_{30}, time of patch removal), as well as at 60 (t_{60}), 120 (t_{120}) and 240 (t_{240}) minutes after patch application ***(Table 2)***. Samples were centrifuged at 3000 rpm for 10 minutes, and plasma was stored at -20°C until analysis. Lidocaine remained stable for 48 hours at room temperature (20°C), ensuring reliable quantification. Analysis was conducted at the BELAC-accredited UZ Brussel lab using validated liquid chromatography with photodiode array detection (Lower Limit of Quantification; LLOQ = 0.01 mg/L) (38). Lidocaine identity was confirmed by UV spectrum matching. The precision of this technique, expressed as the coefficient of variation (CV%), was 6.3% at 0.286 mg/L and 4.1% at 0.072 mg/L, with lower percentages indicating higher measurement reproducibility. Values of detectable lidocaine plasma concentrations that were below the LLOQ were set at 0.005 mg/L. When concentrations exceeded 0.100 mg/L, the treating physician was notified; individual participation was immediately discontinued if levels reached 0.500 mg/L. If plasma lidocaine concentrations reached ≥ 1.000 mg/L in any sample

from any subject, enrolment of new participants was to be discontinued immediately. Lidocaine concentrations were disclosed to investigators on a per-patient basis only after inclusion and were accessible solely within restricted sections of the patient records. All lidocaine plasma concentrations (y-axis) were plotted against measurement time point (x-axis) to visually identify potential outliers relative to the predefined safety threshold of 0.100 mg/L - corresponding to one-tenth of the lowest concentration associated with potential clinical effects in adults or presumed toxicity in young children (1,39). Subsequently, each patient's maximum concentration (Cmax) was compared to the clinical safety threshold using the Wilcoxon signed-rank test.

Adverse events

Based on commonly reported side effects in the literature (2,19,40), local adverse events were defined as skin erythema, oedema, and blanching. These adverse events were assessed at the times of blood sampling ***(Table S2)*** *and* scored from 0 to 4 according to a primary skin irritation system ***(Table S3)***(41). Monitoring of possible systemic adverse events was performed at the same time intervals, and defined as abnormal vital signs: oxygen saturation, respiratory rate, heart rate and -rhythm, blood pressure, body temperature, diuresis, and level of consciousness. All study subjects remained under monitoring and medical supervision at least eight hours after application of the patch (28).

Feasibility study

Caregivers who performed the patch application and removal, rated its usability on a five-point Likert scale (1 = very poor; to 5 = excellent) using a predefined questionnaire (42). The questions addressed ease of application, patch size, adhesion, ease of removal after 30 minutes, and caregiver's assessment of the child's pain during removal.

Statistical Analysis

Statistical analysis was performed using RStudio version 2023.9.1.494 (RStudio, Boston, MA, USA). Based on a power analysis for a one-sample t-test (two-sided, $\alpha = 0.05$, power = 80%), a sample size of 100 patients allows us to detect a difference of 0.03 mg/L between the observed mean peak plasma concentration and the predefined safety threshold of 0.1 mg/L, assuming a standard deviation of 0.107 mg/L (Cohen's d=0.28). As all plasma concentration variables deviated from a normal distribution, they

are presented as medians with first and third quartiles [Q1-Q3]. Likert scores are reported as mean ± standard deviation (SD). Categorical variables are reported as frequencies and percentages. A two-sided p-value < 0.05 was considered statistically significant. Based on physiological and pharmacokinetic considerations, subgroup analysis tested primary outcome differences after stratification by age (0–6 months, 6–12 months, 12–36 months), sex (male, female), ethnicity (Caucasian, Middle East and North African (MENA), Black African), weight-for-height ratio (WFH; Z-scores based on standardized growth curves from birth to maturity in Flanders, Belgium (43): $Z < -1$, $-1 < Z < +1$, $Z > 1$), vascular access type (central venous, arterial), patch application site (elbow fold, upper leg, lower back, back of the hand, suprapubic, foot). Differences in Cmax between subgroups were initially assessed using the Mann–Whitney U test for two-group comparisons and the Kruskal–Wallis test for variables with three or more categories. To further evaluate the association between demographic and procedural variables and Cmax, univariable linear regression analyses were performed, followed by multivariable models adjusted for weight-for-height ratio. For categorical predictors, regression models provided β coefficients and p-values for each subgroup level, while an overall (global) p-value for the variable was obtained from Type III sum-of-squares ANOVA. Subgroup differences in adverse event occurrence were evaluated using Fisher's exact test, and Likert scale scores were compared using the Student's t-test for two groups or the Kruskal–Wallis test for three or more groups.

Ethical considerations

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the local Ethics Review Committee of Universitair Ziekenhuis Brussel and the Belgian Federal Agency for Medicines and Health Products (EUDRACT:2019-002094-55). Written informed consent was obtained from legal guardians of the patients. This study was conducted under the supervision of the Clinical Trials Office (Studieloket) at UZ Brussel, ensuring compliance with medical and ethical standards for interventions in young patients.

RESULTS

Study population

Of 106 eligible patients meeting all inclusion criteria, 72 initiated the study while 34 legal guardians declined informed consent before or during the study for personal reasons. Five patients were excluded afterwards because of incomplete data: two due to unprocessed samples, two because of insufficient sample collection, and one after catheter dislocation during sampling. This resulted in 67 included patients (median age: 0.55 [0.13 – 1.09] years; age range: 3 days to 3 years; 58.2% male). Baseline characteristics are shown in **Table 1**.

Safety study

Distribution of lidocaine plasma concentrations at multiple time points is illustrated in **Figure 1**. Median plasma lidocaine concentrations at time points t_{-15}, t_{15}, t_{30}, t_{60}, t_{120} and t_{240} were 0.005 [0.005–0.005] mg/L, 0.005 [0.005–0.005] mg/L, 0.018 [0.005–0.036] mg/L, 0.020 [0.005–0.031] mg/L, 0.016 [0.005–0.029] mg/L and 0.013 [0.005–0.026] mg/L respectively. Cmax was 0.025 mg/L [0.014–0.038]. Cmax occurred in 2 patients (3%) at t_{15}, in 33 (49%) at t_{30}, in 9 (13%) at t_{60}, in 8 (12%) at t_{120}, and in 15 (22%) at t_{240}. Cmax, as well as concentrations at all measured time points, was significantly lower than the safety threshold ($p<0.001$). This finding was consistent across all demographic and procedural subgroups ($p<0.001$). Only 2 patients exceeded the safety threshold (Cmax 0.270 mg/L at t_{15} and 0.110 mg/L at t_{30}) without any clinical repercussions. In both cases, the concentrations dropped significantly to 0.049 mg/L by t_{30} and 0.030 mg/L by t_{60}, respectively.

Safety analysis across subgroups is illustrated in **Table 2.** No differences in Cmax were observed after stratifying for age, sex, WFH, ethnicity, vascular access type, or patch application site. Although slightly higher median Cmax values were observed in the youngest group (0–6 months: 0.030 [0.017-0.038] mg/L) compared to the 6–12 months (0.024 [0.0211-0.03] mg/L) and 12–36 months group (0.019 [0.014-0.04] mg/L), this difference was not statistically significant ($p=0.512$). Additionally, univariable regression, and multivariable regression adjusted for WFH, showed no associations between age, sex, WFH, ethnicity, vascular access type, or patch application site with Cmax.

Adverse events

No serious patch-related adverse events were observed. Five patients did show systemic effects (notably fever, desaturation, and vomiting), but all in the context of their illness leading to their hospitalisation at the time of inclusion, as confirmed by the supervising physician. Local adverse events occurred in 49 patients (73.1%), manifesting exclusively as local erythema. Among these, two cases (4.1%) were rated as more than moderate in severity. All local adverse events resolved spontaneously within 30 minutes after patch removal, except for seven patients in whom symptoms persisted slightly longer but decreased in intensity. **Table 3** presents the occurrence of local adverse events across subgroups stratified by age, sex, weight-for-height category, ethnicity, vascular access type, and patch application site. Local erythema occurred significantly more frequently in Caucasian (33/40 (83%)) and MENA patients (17/23 (74%)) as compared to Black African patients (0/4 (0%)) (p=0.003). No significant differences were observed in the other subgroup comparisons.

Feasibility

Overall satisfaction of patch application ease, adherence, and ease of removal were rated by caregivers as “at least 4 out of 5” in 58 patients (86.6%) at patch application and in 55 patients (82.1%) at patch removal, with mean Likert scores of 4.48 ± 0.84 and 4.37 ± 0.92, respectively. The mean Likert scores at 0 and 30 minutes for the first age group (0-6 months) were 4.25 ± 0.95 and 4.22 ± 1.01. The second (6-12 months) and third (12-36 months) age group scored 4.62 ± 0.81 and 4.31 ± 1.01; and 4.74 ± 0.56 and 4.68 ± 0.58, respectively. There was no significant difference between the Likert scores compared among age groups, using a one-way ANOVA test and at 0 minutes ($p = 0.097$) and 30 minutes ($p = 0.210$). **Table 4** presents feasibility study across subgroups stratified by age, sex, weight-for-height category, ethnicity, vascular access type, and patch application site. None of these were statistically significant.

DISCUSSION

Safety

In 49% of cases, maximum lidocaine concentrations were observed at the 30 minutes, and in 78% within the expected two hours (17). In 22% of patients, however, the peak occurred at 240 minutes, reflecting a slow accumulation of lidocaine despite a very gradual rise. Plasma concentrations did not return to zero (LLOQ 0.01 mg/L), with 62% of patients (n=42) remaining above 0.005 mg/L after four hours, consistent with previous reports showing that baseline levels may persist for up to 24 hours post-application (17). Due to ethical constraints, no more than six blood samples were collected per patient. Since the primary objective was to evaluate safety in relation to Cmax, the consistent decline in plasma concentrations without secondary rises supports the reassuring safety profile of the patch.

The maximum lidocaine plasma concentrations measured in this study remained well below toxic levels reported in the literature (44,45). Lidocaine concentrations exceeded our own defined 0.100 mg/L strict safety threshold in only two patients, with Cmax values of 0.110 and 0.270 mg/L at 30 minutes post-application. Both remained asymptomatic with no clinical repercussions, and levels quickly fell below the threshold. This safety threshold should be viewed as a very conservative guideline rather than an absolute toxicological cutoff, highlighting the need for careful clinical monitoring in paediatric patients (46). Transient, isolated elevations within expected pharmacokinetic variability and analytical uncertainty are not necessarily indicative of safety concerns. Notably, the 0.110 mg/L concentration may be affected by measurement variability, since the precision of the HPLC-UV method ranges from 1.4% to 7.9%, with accuracy between 91.7% and 106.5% (47). With ~5% precision, 0.110 mg/L corresponds to 0.105–0.116 mg/L, marginally exceeding the threshold. Both cases occurred in patients from the youngest age group; nonetheless, no statistically significant differences in Cmax were detected between age groups. These findings contrast with previous data suggesting an inverse correlation between age and lidocaine exposure, though that study included merely four children under the age of three (27).

Adverse events

Erythema occurred in three-quarters of patients, most likely due to the vasodilatory effect and local warming of the patch (9,18,20). This aligns with previous studies but shows a higher prevalence than reported in older children (~30%)(2) and adults (3–10%)(40). The increased sensitivity in younger children may be attributed to differences in skin pharmacokinetics, including a higher surface area-to-body weight ratio (1,31), although in this study no significant difference in erythema occurrence was observed between age groups ($p=0.544$). Other known application site reactions (32) - such as rash, pruritus, or blisters - were not observed. In patients with dark skin, erythema was not observed likely because pigmentation hindered accurate detection, which may result in cases going unnoticed (48). No serious patch-related adverse events were observed, consistent with previous studies (11,18,21,22).

Feasibility

The 0–6 months age group received a lower mean Likert score at both patch application and removal, indicating some dissatisfaction when compared to older groups. Caregivers commented that the patch size was not suited to the smaller body surface of this group. In six patients (four in age group 1, one in age group 2, and one in age group 3), the patch was oversized and failed to adhere properly, loosening within 30 minutes. However, these findings did not affect the overall positive satisfaction rate.

Limitations

An interim post-hoc power analysis was performed after two-thirds of the target sample had been enrolled. Based on the observed effect size ($d = 0.89$, $\mu = 0.033$, $SD = 0.037$) and assuming $\alpha = 0.05$, the analysis yielded a power estimate >0.999. This suggests that the achieved sample size was more than sufficient to detect the observed effect, indicating that the study was unlikely to have been underpowered. The study was therefore concluded with 67 inclusions on January 30, 2025, retaining adequate power to support its conclusions, despite the smaller sample than originally planned.

One protocol deviation involved a patient weighing 2.88 kg, who remained clinically stable and gained 9.9% body weight within two weeks, minimizing impact on study validity. Nine patients had haemoglobin levels below the protocol threshold of 11 g/dL; all were clinically stable, showed increasing haemoglobin trends, and were monitored in subsequent samples. These deviations were not considered to have affected study outcomes.

No significant associations were found between mean Cmax and independent variables (sex, ethnicity, vascular access, or application site), corrected for weight-for-height ratio. While prior studies suggest that percutaneous absorption inversely correlates with stratum corneum thickness (10,11,31) and may vary with skin pigmentation (49), subgroup sizes in our cohort - particularly patients with dark-pigmented skin (n=4) and less common application sites (e.g. foot [n = 4], suprapubic region [n = 6]) - were too small to draw definitive conclusions. These analyses were underpowered and should be considered exploratory. The exact time of Cmax could not be determined due to fixed sampling intervals, possibly missing intermediate peaks. As a result, Cmax and erythema may not have occurred simultaneously, preventing accurate analysis of their association.

Concentrations of MEGX, lidocaine's primary hepatic metabolite, were not measured in this study, but previous research did not indicate that transdermal lidocaine absorption from heated patches induces toxicity (17,28,50). A lidocaine/MEGX ratio of 4:1 has been reported in healthy adults after applying three topical patches simultaneously. If similar ratios occurred here, total active compound exposure would remain below toxic lidocaine thresholds (50).

Tetracaine concentrations were not measured due to its rapid degradation by plasma esterases (1,33). Although sample handling on ice, prompt processing at 4°C, freezing, or adding esterase inhibitors could reduce breakdown (18,47,51), these measures were impractical and do not guarantee detection. Tetracaine's short half-life affects sampling timing but not analysis. Whether plasma levels fell below the PDA method's LLOQ remains untested and unvalidated.

CONCLUSION

The use of the S-Caine Patch in children under three years is safe, with plasma lidocaine concentrations remaining well below safety thresholds, and with only transient minor local adverse events observed. Feasibility was rated positively, although improvements in patch size and adhesion for this age group are needed to enhance usability in case of painful procedures.

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None.

DISCLOSURES

None.

DATA AVAILABILITY STATEMENT

Anonymised data will be made available in the RedCap registry.

AUTHORS' CONTRIBUTION

BA contributed to the methodology, formal analysis, investigation, patient inclusion, data curation, project administration, original draft writing, and visualization. TDP contributed to data analysis, statistics, and review. RB contributed to the power and formal analysis and supervision. KL contributed to lab analysis and provided resources. GvB contributed to conceptualization, methodology, patient inclusion, project administration, supervision, and review & editing.

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