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Original Article

A comparison of Rapydan® patch and Ametop® gel for venous cannulation*

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Summary

Ametop® gel (4% tetracaine) is used to provide topical anaesthesia for venous cannulation. Rapydan® patch (7% lidocaine and 7% tetracaine) has been developed to provide topical anaesthesia by a different mechanism, that of heat assisted delivery. We compared the topical anaesthetic effect of these agents for venous cannulation. One hundred healthy adults undergoing day-case surgery were randomly assigned to receive either Rapydan (n = 50) or Ametop (n = 50) before venous cannulation. Pain on insertion was scored on a visual analogue scale between 0 and 100 (where 100 = unbearable pain). Median(IQR[range]) pain scores were not different between groups with 11 (5–20 [0–72]) for Rapydan and 10 (5–24 [0–95]) for Ametop (p = 0.63). Adequate topical anaesthesia was achieved in over 90% of patients in both groups. Rapydan produces topical anaesthesia comparable with Ametop for venous cannulation.

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Venous cannulation causes pain and discomfort. Local infiltration with lidocaine can relieve pain although its administration can be painful. Topical anaesthetic agents applied locally to the vein before cannulation are non-invasive, but have a slower onset of effect. The two commonly used topical agents are Eutectic Mixture of Local Anaesthetics (EMLA™) cream (lidocaine 2.5% with prilocaine 2.5%; Astra Zeneca UK Ltd, Luton, Bedfordshire, UK) and Ametop® gel (4% tetracaine; Smith & Nephew Healthcare Ltd, Hull, UK). Both preparations have been widely used for topical anaesthesia during cannulation in the last decade [1, 2]. A major disadvantage of these agents is the time delay to effectiveness (up to 1 h) and the reported side effects of vasoconstriction and blanching with EMLA, and rash and methaemoglobinaemia with Ametop [3].

Rapydan® (Eurocept Group, Trapgans 5, 1244 RL Ankeveen, The Netherlands) is a medicated patch containing a mixture of 7% lidocaine and 7% tetracaine. It has a novel method of drug delivery using a control heat assisted drug delivery (CHADD) system [4]. The patch is activated when exposed to air, which produces a chemical reaction warming the skin up to a maximum temperature of 40 °C soon after its application. This heating effect is designed to enhance the delivery of local anaesthetics through the skin [5] giving a relatively rapid onset of action. Thirty minutes after application, the average depth of topical anaesthesia is reported to be greater than 3.6 mm [4]. The Rapydan patch contains a

eutectic mixture and it is claimed that it provides a more rapid onset of topical anaesthesia compared with non-thermogenic formulations [4].

Since its introduction into clinical practice, Rapydan has been used primarily to prevent pain during vascular access procedures [6, 7], but has also found various applications including use for minor dermatologic procedures [8] and epidural catheter placement [9]. Comparison with EMLA cream has shown Rapydan to offer superior analgesia [4]; however, comparison between EMLA and Ametop has suggested the latter to be superior [2]. There is no published comparison between Ametop and Rapydan. This study compares these two formulations for pain relief during venepuncture.

Method

With the approval of to Leeds (West) Local Research Ethics Committee and with Medicines and Healthcare products Regulatory Authority authorisation, we conducted a double-blind, randomised, controlled trial of 100 patients of ASA physical status 1-2, of both sexes, aged 18-65 years. All patients gave fully informed written consent. Eligible patients needed to have viable veins on the dorsum of the hand and to be listed for day-case surgery. Exclusion criteria included pregnant or lactating females, patients with a known history of methaemoglobinaemia, anaphylaxis or drug allergy, or those taking anti-epileptics, anti-arrhythmics, or analgesic medication.

The randomisation code was generated by the Pharmacy Clinical Trials Department at Leeds General Infirmary. Randomisation was performed by enclosing the study drug in a sealed white box along with the data collection sheet, an 18-G cannula, cannulation pack and gauze bandage for concealment. In addition, boxes containing Ametop contained an occlusive dressing for its application. Fifty boxes containing Rapydan and 50 containing Ametop were prepared by the unblinded clinical trials pharmacist. Externally there was no way of determining the content of the sealed packed boxes apart from the unique identifier number present on package labelling. This identifying code corresponded to a treatment group that was only known to pharmacy until the trial's end.

All cannulations were performed by the designated single skilled operator from the research team (NR). Before application of the study drug the dorsum of the patient's hand was inspected and an appropriate vein for cannulation selected and marked using a surgical pen. An unblinded, independent, trained nurse then applied the study drug locally to the marked area in the absence of the investigator. To do this, patients were asked to present their hand and turn their heads away and shut their eyes so that they could not observe the intervention. The nurse then opened the study drug box and applied the contained application whilst keeping the data collection sheet, cannula and cannulation pack. In all cases the study application was then concealed from the patient by wrapping gauze bandage over the area.

The allocated treatment was applied for 45 min (with 40–50 min being considered an acceptable range for duration of application), after which, again in the absence of the investigator, patients were asked to turn their heads away and close their eyes whilst the application was removed. The investigator then cannulated the vein with an 18-G cannula (Vasofix® Safety; BBraun, Meisungen, Germany).

Before cannulation the application area was inspected for vasoconstriction, erythema and oedema and each was individually assessed on a 4-point scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe. The time from application of treatment to cannulation was noted. A visual analogue score (VAS) between 0 and 100 mm (where 0 = no pain and 100 = unbearable pain) was used to gauge patients' reported pain. A descriptive pain score (no pain, pressure, dull pain, sharp pain) was also used and patients were asked whether they would recommend the treatment and whether they felt that it provided adequate anaesthesia. Any adverse or serious adverse events were documented. If cannulation failed, or patients felt intolerable pain during cannulation, an option of 0.5 ml lidocaine 1% infiltration was available for rescue medication at an alternative site.

Manufacturers' information suggested that the proportion of patients experiencing no pain at 30 min was 60% with EMLA and 90% with Rapydan. This difference was considered clinically significant. Sample size calculation was based on the detection of a similar difference between Ametop and Rapydan. A sample size of 50 per group would have a 90% power at a 5% significance level to detect such a difference; even allowing for 20% losses this would still leave power greater than 80%. Differ-

ences in VAS were tested using the Mann–Whitney test, as previous results suggested that this was unlikely to be normally distributed. A value of $p < 0.05$ was considered significant. All results were analysed using Statistical Package for Social Sciences (SPSS version 15; SPSS Inc, Chicago, IL, USA).

Results

One hundred patients were randomly allocated into the study, 50 per group. Two patients in the Rapydan group and another in the Ametop group withdrew from the study after drug application, but before cannulation, stating 'fear of the unknown'. Patients' characteristics are summarised in Table 1. The total number of evaluable patients was 97. Venous cannulation was achieved on the first attempt in 96 patients. Rescue analgesia was given to one patient from Ametop group following initial failed cannulation and VAS assessment. This patient required two further cannulation attempts.

Visual analgoue scores for pain were comparable between groups (Table 2). Four patients in the Ametop group and one in the Rapydan group had high scores and were considered as outliers, but nevertheless included in the analysis. Descriptive pain scores were also comparable between groups (Table 2). Adequate topical anaesthesia was reported from more than 90% of patients for both drug applications and the majority of patients recommended the treatment for future venous cannulation.

Following application of Rapydan and Ametop, vasoconstriction was not observed over the local area in 83% and 74% patients, respectively. This difference was not statistically significant. No erythema or oedema was observed and no adverse or serious adverse events occurred in either group.

Table 1 Characteristics of patients receiving Rapydan or Ametop before cannulation. Values are mean (SD) or number.

	Rapydan (n = 50)	Ametop (n = 50)
Age; years	39 (12)	41 (13)
Sex; F:M	23:27	22:28
Weight; kg	72 (15)	75 (16)
ASA physical status; 1:2	40:10	33:17
Duration of application; min	50 (3)	49 (4)

Table 2 Pain experienced by patients receiving Rapydan or Ametop before cannulation. Values are median (IQR [range]) or number (proportion).

	Rapydan (n = 48)	Ametop (n = 49)	p value
VAS	11 (5–20 [0–72])	10 (5–24 [0–95])	0.63
Descriptive pain score			
No pain	7 (15%)	7 (14%)	0.16
Pressure	12 (25%)	10 (21%)	0.11
Dull sensation	7 (15%)	6 (12%)	0.30
Sharp pain	22 (45%)	26 (53%)	0.35

VAS, visual analogue score.

Discussion

There were no significant differences in the performance of Rapydan and Ametop for venous cannulation for any of the parameters investigated. It is possible that patients could have become aware of their treatment group by the sensation felt after application. It is, however, unlikely that any of the patients enrolled had intimate knowledge of topical anaesthetic preparations and hence, would have remained unbiased even if unblinded. However, the research team did not ask the participating patients whether they had any previous exposure to either of the study drugs.

For venous cannulation, the onset of action for Rapydan is 30 min and for Ametop it is 45 min. To ensure that the trial could be conducted in a double-blind fashion, application time was standardised to 45 min (with 5 min above or below this considered acceptable). Both applications remain effective after 1 h [5, 10]. This trial compared the analgesic effect of the two applications and not the time of onset. It is widely accepted that Rapydan has a more rapid onset than other available topical anaesthetic agents [5]. This benefit, however, must be balanced against cost, with Rapydan being over five times more costly than Ametop [10].

This study standardised the size of cannula used. The 18-G cannula could be argued to cause more pain than a smaller gauge, but the investigators felt this to be a very widely used size. The authors considered that both treatment groups would benefit from a local anaesthetic effect [10].

Cutaneous vasodilatation has been reported earlier with the topical application of Rapydan [4], associated

with the release of heat, histamine and 5-hydroxytryptamine. We did not evaluate vasodilatation in the study. This study employed a single operator, again to increase uniformity. Vasoconstriction was observed by our single observer in 17% of the Rapydan and 26% of the Ametop group, although the degree of constriction was not assessed. This appears to be consistent with the findings of a healthy volunteer trial measuring Laser doppler blood flow, where Ametop was shown to increase microvascular flow greater than Rapydan [11].

Both drugs were well tolerated and none of the patients had erythema or oedema on assessment. This was contrary to the findings of previous studies [4, 5] where erythema, oedema and blanching were common skin reactions with Rapydan. We are unable to account for this discrepancy and our use of a single operator should have ensured consistency of our reporting.

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