Efficacy and Safety of Vapocoolant Spray during Repeated Needle Stick Of Rat Pups Hindpaws

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INTRODUCTION

Infants have blood drawn frequently in the NICU for screening/ diagnostic tests and heel-lance accounts for 2/3 of these tests. Neonatal exposure to repetitive poorly managed pain at a crucial time of the nervous system development may trigger adverse behavioral and neurodevelopmental outcomes. Opioid/NSAIDs analgesics in newborns may cause cardiorespiratory depression and adverse effects with repeated administration on brain development. Given that the infants are denied analgesics and ineffectiveness of the topical anesthetics for heel glabrous skin, we previously demonstrated analgesic effectiveness of a the topical vapocoolant spray on the hind paw of rat pups. We hypothesized that the 1) Vapocoolant spray prolongs the latency time of reflex flexion withdrawal of rat pup hindpaws in response to heat pain after application by two methods; method I (MI) 4-second application at 3 inches distance and in method II (MII) 10-second application at 7 inches distance. 2) Repeatedly applications on a single hind paw before heel-lances will not produce histopathological toxicity.

METHODS

After IRB approval, we used awake Sprague-Dawley rat pups aged 7 days old, both male and female a total of 64 rat pups in efficacy and 40 in toxicity study. For efficacy 32 rat pups were included in MI and 31 in MII. The vapocoolant was randomly applied once to one hindpaw and saline on the other. Heat pain sensitivity to spray was measured by contact with a hotplate device. For toxicity, 20 rat pups were assigned to either MI or MII. After each application, heel-lance was performed with the use of BD Quikheel™ Lance. This procedure was performed 3 times daily for 2 days.

Efficacy: Vapocoolant spray was applied randomly to either the left or right hindpaw of 32 rat pups in M I and 31 rat pups in M II treatments and the contralateral hindpaw was treated with saline (placebo). The treatments were sprayed continuously and allowed to take effect over 45 seconds before subjecting each paw to the hotplate test. Heat pain sensitivity to spray treatments was measured by changes in nociceptive flexor withdrawal (NFW) latency time (seconds) in contact with a hotplate using a modified hotplate test. The latency with which the paw was withdrawn was recorded by blinded research assistant. This test was repeated 3 times at 10-second intervals at baseline and 3 more times after treatment with study sprays. After completion of the study, rat pups were returned to their dams for breastfeeding until euthanasia on day 7.

Safety: A single investigator applied the vapocoolant spray in M I (n=20) to one hindpaw either on left or right hindpaw randomly and used the contralateral paw as control. Forty-five seconds after each application heel stick was performed with the use of BD Quikheel™ device. This procedure was performed 3 times daily for 2 days on the same paw. Similar procedure was performed on 20 rat pups of M II. The repeated sticks were performed on the hindmost part of the paw over the lateral or medial plantar margins of previously un-incised area and to avoid contact with calcaneus.

Table 1. Treatment Effect for Each Method.

Treatment	Saline	Vapocoolant	p-value
Method I	1.13 (0.24)	1.88 (0.74)	<0.001
Left side	1.15 (0.27)	2.15 (0.77)	<0.001
Right side	1.11 (0.22)	1.61 (0.62)	<0.001
Method II	1.38 (0.54)	9.42 (3.23)	<0.0001
Left side	1.22 (0.54)	8.93 (3.25)	<0.0001
Right side	1.56 (0.50)	9.95 (3.23)	<0.0001

Data are mean (SD) in seconds with ANOVA comparisons.

Table 2. Method Effect.

Method	Method I	Method II	p-value
Saline	1.13 (0.24)	1.38 (0.54)	0.021
Left side	1.15 (0.27)	1.22 (0.54)	0.638
Right side	1.11 (0.22)	1.56 (0.50)	0.004
Vapocoolant	1.88 (0.74)	9.42 (3.23)	<0.0001
Left side	2.15 (0.77)	8.93 (3.25)	<0.0001
Right side	1.61 (0.62)	9.95 (3.23)	<0.0001

Data are mean (SD) in seconds with ANOVA comparisons.

DICUSSION

Both MI and MII significantly increased heat pain thresholds relative to saline but the magnitude was significantly greater with MII vs. MI by 4 folds. There were no pathology identified in the 40 hindpaws. This is the first study to demonstrate effectiveness and safety of a topical anesthetic on glabrous skin. We plan to expand the investigation to determine if the effectiveness would minimize the negative brain neuroimaging findings observed in NICU infants after repeated heel-lancing without the benefit of analgesia.

CONCLUSION

Although it is difficult to translate the rat pup data to human infants the safety and efficacy data of this study is encouraging and deserves exploration in neonatal clinical trials.

REFERENCES

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