Author(s): VS/AT
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Question: Should topical anesthetics vs placebo/control be used for reducing vaccine injection pain in children 0-12 years?[1,2,3,4]
Settings: clinics, schools
Bibliography: Abuelkeir 2014, Achema 2011 (2), Basiri-Moghadam 2014, Cassidy 2001, Cohen 1999 (2), Cohen 2006 (3,4), Cohen Reis 1997 (2), Dilli 2009 (2), Gupta 2013 (1), Halperin 2000, Halperin 2002, Kumar 2014, O'Brien 2004 (2004 thesis), Taddio 1994, Uhari 1993

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical anesthetics	Placebo/control	Relative (95% CI)	Absolute		
Pain [5] (measured with: validated tools (Faces Pain Scale 0-6); Better indicated by lower values)												
3	randomised trials	very serious[6]	no serious inconsistency[7]	no serious indirectness	serious[8]	none	138	131	-	SMD 0.29 lower (0.64 lower to 0.05 higher)[5]	⊕OOO VERY LOW	CRITICAL
Pain (yes/no) (assessed with: validated tool (Faces Pain Scale, yes/no))												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	14/83 (16.9%)	33/76 (43.4%)	RR 0.39 (0.23 to 0.67)	265 fewer per 1000 (from 143 fewer to 334 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Fear (measured with: validated tool; Better indicated by lower values)												
1	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	34	34	-	SMD 0.04 higher (0.29 lower to 0.37 higher)	⊕OOO VERY LOW	CRITICAL
Distress Pre-procedure (measured with: validated tool (Child Facial Coding System 0-19, Children's Hospital of Eastern Ontario Pain Scale 4-13) by researcher; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	81	71	-	MD 0.22 lower (0.54 lower to	⊕⊕⊕O MODERATE	CRITICAL

										0.1 higher)		
Distress Pre-procedure + Acute[10] (measured with: validated tool (Modified Behavioural Pain Scale 0-10) by researcher; Better indicated by lower values)												
1	randomised trials[11]	very serious[12]	no serious inconsistency	no serious indirectness	serious[8]	none	42	42	-	SMD 0.14 higher (0.29 lower to 0.56 higher)[10]	⊕OOO VERY LOW	CRITICAL
Distress Acute[13,14,15] (measured with: validated tools (Modified Behavioural Pain Scale 0-10, Visual Analog Scale 0-10, Child Facial Coding System 0-19, Children's Hospital of Eastern Ontario Pain Scale 4-13, Neonatal Infant Pain Scale 0-7, Modified Facial Coding Score 0-6, Neonatal Facial Coding System 0-10, Pain Assessment in Advanced Dimentia modified 0-10) by researcher, clinician, parent; Better indicated by lower values)												
13	randomised trials	very serious[6,16]	no serious inconsistency[17]	no serious indirectness	no serious imprecision	none	714	710[14]	-	SMD 0.91 lower (1.36 to 0.47 lower)[13,14,15]	⊕⊕OO LOW	CRITICAL
Distress Acute (yes/no) (assessed with: validated tool (Neonatal Infant Pain Scale 0-7) by researcher)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	1/7 (14.3%)	7/7 (100%)	RR 0.20 (0.05 to 0.86)	800 fewer per 1000 (from 140 fewer to 950 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Distress Acute + Recovery (measured with: validated tool (Cry duration) by researcher; Better indicated by lower values)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	273	273	-	SMD 0.68 lower (1.24 to 0.13 lower)	⊕⊕⊕O MODERATE	CRITICAL
Distress Acute + Recovery (yes/no) (assessed with: validated tool (Cry, yes/no) by researcher)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	115/168 (68.5%)	138/168 (82.1%)	RR 0.84 (0.75 to 0.93)	131 fewer per 1000 (from 57 fewer to 205 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Distress Recovery (measured with: validated tools (Modified Facial Coding Score 0-6, Modified Behavioural Pain Scale 0-10) by researcher; Better indicated by lower												

values)												
2	randomised trials	no serious risk of bias	serious[18]	no serious indirectness	serious[8]	none	105	105	-	SMD 2.15 lower (4.68 lower to 0.37 higher)	⊕⊕OO LOW	CRITICAL
Distress Pre-procedure + Acute +Recovery [19] (measured with: validated tool (Child-Adult Medical Procedure Interaction Scale-Revised) by researcher; Better indicated by lower values)												
1	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[8]	none	34	34	-	SMD 0.19 higher (0.14 lower to 0.52 higher)[19]	⊕OOO VERY LOW	CRITICAL
Distress Acute (observer report for child) (measured with: validated tools (Visual Analog Scale 0-10, Faces Pain Scale 0-6) by parent/nurse ; Better indicated by lower values)												
1	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	serious[9]	none	21	21	-	SMD 1.13 lower (1.78 to 0.47 lower)	⊕⊕OO LOW	
Safety (skin reactions) (assessed with: observation of site for pallor, erythema (yes/no) by researcher)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	51/80 (63.8%)	11/79 (13.9%)	RR 3.09 (0.51 to 18.59)	291 more per 1000 (from 68 fewer to 1000 more)	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Safety, Pallor [21] (assessed with: observation of site for pallor (yes/no) by researcher)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	187/442 (42.3%)	78/439 (17.8%)	RR 2.59 (1.56 to 4.29)[21]	283 more per 1000 (from 99 more to 585 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
Safety, Erythema[21] (assessed with: observation of site of erythema (yes/no) by researcher)												
5	randomised	no serious	no serious	no serious	no serious	none	129/442	87/439	RR 1.42 (0.99 to	83 more per 1000 (from 2	⊕⊕⊕⊕	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	imprecision		(29.2%)	(19.8%)	2.03)[21]	fewer to 204 more)	HIGH	
								0%		-		
Safety (immunogenicity) [22] (assessed with: validated tools (protective antibody titre))												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	-	-	⊕⊕⊕⊕ HIGH	
								0%		-		
Parent Preference [23] (measured with: validated tool (Visual Analog Scale 0-10 or yes/no) questionnaire about future use; Better indicated by lower values)												
3	randomised trials	serious[24]	no serious inconsistency	no serious indirectness	serious[25]	none	21	21	-	SMD 0.26 lower (0.87 lower to 0.35 higher)	⊕⊕OO LOW	IMPORTANT
Parent Use of Intervention [26,27] (assessed with: visual inspection of application site by researcher)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	-	-	-	-	⊕⊕⊕O MODERATE	IMPORTANT
								0%		-		
Procedure Outcomes, Parent Fear, Vaccine Compliance, Memory, Preference, Satisfaction (assessed with: no data were identified for these important outcomes)												
0	No evidence available					none	-	-	-	-		IMPORTANT
								0%		-		
Parent Fear Acute (measured with: validated tool (Visual Analog Scale 0-10); Better indicated by lower values)												
1	randomised trials	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	21	21	-	SMD 0.50 lower (1.11 lower to 0.12 higher)	⊕⊕OO LOW	IMPORTANT

[1] In study by Cohen (1999), a cross-over design was used whereby children received 3 treatments (video distraction, topical anesthesia, or no treatment). Cohen 1999 (2) compares topical anesthesia to no treatment.

[2] In study by Cassidy (2001) and Taddio (1994), parents applied the topical anesthetic at home prior to coming to the clinic. In study by Taddio (1994), 91% of parents reported it was easy to apply the cream.

[3] In 9 included studies, vaccines were administered intramuscularly; in 2 studies, they were administered subcutaneously; in 2 studies both intramuscular and subcutaneous vaccines were given; and in 1 study both intramuscular and intradermal vaccines were given.

[4] In 5 of the 14 included studies (Achema 2011, Basiri-Moghadam 2014, Cohen 1999, 2006, Dill 2009), there was a no treatment control group; in 1 study (Kumar 2014) there was a water spray control group; the remaining 8 studies included a placebo control group.

[5] In study by Cohen 1999, there was a high risk of bias due to lack of blinding, co-intervention and vaccination of children in groups. Removal of the data from this study alters the

meta-analytic result: SMD -0.47 (95% Confidence Interval -0.73, -0.21).

[6] In one study (Cohen 1999), there was no blinding and there was co-intervention bias - more distraction delivered in the comparison (no treatment control) group. In study by Cohen Reis (1997), immunizers and outcome assessors were not blinded.

[7] Heterogeneity can be explained by differences in study design and quality (blinding vs. no blinded) and environmental factors (setting of vaccination - school vs clinic; time delay for topical anesthetic delivery; vaccination in groups vs independent; behaviours of immunizers)

[8] Confidence interval crosses the line of nonsignificance and the sample size was below the recommended optimum information size (OIS) of 400 for an effect size of 0.2

[9] Sample size was below the recommended optimum information size (OIS) of 400 for an effect size of 0.2

[10] The sample size/group was assumed to be equal

[11] In study by Cohen 2006 (3,4), analysis (3) compared the intervention (topical anesthesia) to control (no treatment) at 12 months, and analysis (4) compared the intervention (topical anesthesia) to control (no treatment at 18 months). The data are considered independent due to the loss of 50% of the study sample.

[12] Not truly random; immunizer, parent not blinded; outcome assessor blinded

[13] In study by Cassidy (2001), a sample size of 83 was used for the intervention (topical anesthetic) group and 78 for the control (placebo) group

[14] In study by Uhari (1993), 71% of parents reported they hoped the study intervention would be used on the next occasion. For the remainder, reasons for not using the intervention include; inconvenience and discomfort caused by removal of the occlusive dressing.

[15] In study by Abuelkheir 2014, 8/216 participants were 4-6 years; the remainder were 2-24 months

[16] In one study by Achema 2011, there was no blinding

[17] Heterogeneity can be explained by differences in age (6 weeks to 15 years), setting (school, hospital, clinic) and variability in assessment techniques.

[18] Unexplained heterogeneity

[19] Scores not standardized

[20] Immunizers not blinded; outcome assessors not blinded

[21] Analysis includes data from Taddio (1992) in adults

[22] In 3 included studies including 445 infants and children (Halperin 2000, 2002, O'Brien 2004), none demonstrated an effect on antibody titre levels in the topical anesthetic group compared to placebo. The vaccines studied included Measles-Mumps-Rubella, Diphtheria-Tetanus-acellular Pertussis-inactivated Poliovirus-Haemophilus influenza type b, and Hepatitis B. Separately, a controlled trial by Dohlwitz (1998) reported no effect on Bacillus-Calmette-Guerin in 388 children.

[23] In study by Uhari (1993), 106/155 (70%) of parents reported that they preferred the cream be used on the next occasion. In study by Taddio (1994), 84/96 (88%) of parents reported that they could fit the application of the cream in their schedules and 87 (91%) reported that the cream was not difficult to apply. Separately, in study by Cohen Reis (1997) investigating topical anesthetics + distraction vs vapocoolant + distraction vs distraction alone, parents reported they were willing to pay $11.90 for topical anesthetics for future injections.

[24] Immunizer not blinded; outcome assessors not blinded

[25] Small sample size

[26] In study by Taddio (1994), 96/100 (96%) of parents applied the topical anesthetic cream correctly (i.e., adequate quantity of cream, duration of cream application, and occlusion of cream on skin with dressing). In study by Cassidy (2001), 154/161 (96%) of parents applied the topical anesthetic patch correctly (i.e., correct patch application location, duration of patch application, and adherence of patch on skin).

[27] In study by Abuelkheir (2014), the mean waiting time before vaccine injection was 57 minutes (SD = 16.7). Separately, Taddio (2012) reported a mean waiting time of 41.6 minutes (SD = 28.7).