Trends in Topical Local Anesthetics for Venipunture/cannulation

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Goals

- Review
- Options for needle-related procedural pain/distress
  - Non pharmacological & pharmacological
  - Protocols in USA & Europe
- Success rate of various formulation of topical LA
  - Pain relief (measurements), venous access
- Failure to achieve analgesia; alternatives
- Current practice: Pros & cons
- RCT only

Why treat needle-related procedural pain?

ACIP 2004, AAP 2004, AAFP 2004, CPS 2004,
Sethna & Houck Expert Rev. Neurotherapeutics 2005
McGaig et al, Natl Center Health Statis 2004

- A common source of pain & distress for healthy/ill
  - Most children find needle-related procedures intrinsically painful, traumatic and aversive
- Premature infants: average 234 painful procedures 1st two wk of life or up to 14 procedures per day
- Recommended over 20 immunizations before age 18 y
- 1/5 patients in ED require venous cannulation
- Repetitive painful stimuli --> poor development

Relief of Pain & Anxiety in Emergency Medical Systems

Committee on Pediatric Emergency Medicine & Section on Anesthesiology & Pain Medicine 2004

- "Topical anesthetics can be placed proactively to control the pain associated with minor procedures"
- "Incorporate pharmacological and non-pharmacological interventions in the standard of care"
- There is interest in finding innovative methods to reduce pain from minor procedures

Why topical anesthesia/analgesia is not used routinely?

- Lack of good-quality evidence on the safety & efficacy of pain relieving strategies
  - Cost
- Belief systems
  - Personal
  - Institutional
  - Religious
  - Cultural
  - Etc.

Non-pharmacological Interventions

- Psychological interventions
  - Efficacy of cognitive &/or behavioral approaches
    - Reasonably good data 2-19 y
    - Infants; head to head comparisons
- Non-psychological interventions
    - E.g., acupuncture, virtual reality, etc.

Psychological interventions for needle-related procedural pain & distress

Uman LS et al., Cochrane review 2006

- 28 RCTs, ; age 2-19 y, n = 1039 Rx, n = 951 controls
- Mostly studied immunizations & injections
- Largest improvement
  - Distraction (self-reported)
  - Combined CBI
  - Behavioral interventions
  - Hypnosis (self-reported) most promising
  - Information/ preparation, distraction with nurse coaching or parent or positioning were promising but of limited evidence

Efficacy & Safety of Sucrose for Heel-lance in Pretem and Term Neonates during first week of life (R, PC, DB) *Gibbins et al, Nursing Research 2002*

	Sucrose + NNS (n = 64)	Sucrose (n = 62)	Water (n = 6)
GA (wk)	33.7 ± 3.8	33.9 ± 3.8	33.7 ± 4
Wt (kg)	2.2 ± 0.9	2.3 ± 1	2.2 ± 0.9
SNAP	Should be the standard of care in NICU		
No. of painful procedures	11.9± 2	11.6± 2	11.9 ± 1.6
Procedure duration (min)	11 ± 1.7	10.7 ± 1.2	10.9 ± 1.3
Mean PIPP at 30, 60 s	8.2, 8.9*	9.8, 11.2	10.2, 11.2
Side effects	3	2	2

24%, 0.5mL 2 min; SE: desaturation < 80% self-limited

Pharmacological Options for Venipuncture & cannulation [commercially available]

- Infiltration of LA induces pain/needle anxiety
- Eutetic mixture lidocaine-prilocaine 5% cream
- Liposome-encapsulated lidocaine 4%
- Eutetic mixture lidocaine-tetracaine 70% cream
- *Tetracaine gel 4%, liposome-encapsulated*
- Needle-less delivery systems of local anesthetics:
  - iontophoresis, jet-propulsion injectors, sonophoresis, laser assisted analgesia

Pain- & Distress-reducing Interventions for Venepuncture in Children (RCT)

Tak JH et al., Child: Care Health & Development 2006

- Compare the effect of EMLA 5% and a placebo cream during venepuncture in 136 children 3 - 12 y

- Conclusion
  - EMLA 5% reduces pain greater than placebo
  - EMLA 5% reduced pain-related distress during venepuncture
  - Topical LA should be used for venipuncture

Parents' willingness to pay for diminishing children's pain during blood sampling

Wasserfallen et al., Pediatric Anesthesia 2006

- Switzerland; Topical LA prior venipuncture is not reimbursed by insurance company
- Parents were surveyed in out patient clinics
  - Specialized clinic, oncology, emergency
- Parents
  - Were willing to pay a median price close to real drug price

Determinants of Success & Failure of EMLA (R, PC, DB)

Lander et al., Pain 1996

N = 258; Ages 5 - 18 y

- Factors predicting success
  - Success rate (no pain; VAS ≤ 10 / 100 mm)
    - 84% venipuncture vs 51% cannulation
    - EMLA > PL in both venipuncture & cannulation
  - Duration 90 min; venipuncture > venous cannulation
  - More pain with higher anxiety (STAI) Rx & PL
  - Age was not a factor

Liposome-encapsulated Lidocaine 4%, 30 min application for venous cannulation (RCT, DB)

Taddio et al., CMAJ 2005

	Lidocaine	Placebo	P values
N (age 1 m -17 y)	69 (67 ≥ 5 y)	73	
Pain 1st attempt (FPS-R) *patient, parent, research observer*	2.6	3.9	0.001
Success on 1st attempt	74%	55%	0.03
Duration	6.7 min	8.5 min	0.04
Blanching, erythema, itching	23%	23%	NS

(Maxilene, RGR Pharma, Windsor Ont.)

Comparison of Liposomal Encapsulated Lidociane 4% vs EMLA 5% (RCTs)

1. Eichenfield et al., Pediatr 2002 *2.Kleiber et al., Pediatr 2002*

Ref	N (age)	Dose / Duration		Pain intensity	Efficacy
		Lidocaine	EMLA		
1	90 (5 - 17 y)	2.5g 30 - 60 min	2.5g 60 min	VAS	EMLA > liodcaine venipuncture
2	30 (7 - 14y)	2.5g 30 min	2.5g 60 min	Oucher scale	EMLA = liodcaine iv cannulation

Amethocaine 4% ; Systemic Bioavailability

van Kan et al, Am J Health Syst Pharm 1997

- N = 10, ages 1 - 5 years
- Sampling time 30 min after application
- N = 10; **undetectable** in all patients (limit of detection was 0.05 mg/L)
- N = 7; BBA (--> PABA) detected 0.05 - 1.8 mg/L (limit of detection 0.05 mg/L)

Comparative Studies of Tetracaine gel 4% vs EMLA 5% (RCT)

1.Lawson et al., BJA 1995, 2.Choy et al, Acta Paediatr 1999, 3.Romsing et al, BJA 1999, 4.O'Brien et al., Pediatr 2004

Ref	N (age)	Dose / Duration		Pain intensity	Efficacy
		Tetracaine	EMLA		
1 R, SB	T=55, E=55 (3-12 y)	1g 40 min	2g 40 min	3-point scale (Pt)	T > E venipuncture
2 R, SB	T=17, E=17 (1-14 y)	1g 30-45 min	2g 60 min	OSBD VAS (pt/dr/pr)	T = E venipuncture
3 R, DB	T=20, E=20 (3-15y)	1g 45 min	2g 60 min	Poker chip (pt)	T > E IV cannulaiton
4 R, PC, DB	T= 61, P=59 (1 y)	1g 30 min	1g 30 min	MBPS	T > PL vaccination

R = randomization, PC= placebo control, SB = single blinded, DB = double blinded

Amethocaine 4% Trials in Neonates Gestational Age 27-42 weeks (R, PC, DB)

Ref	N (age)	Dose / Duration	Pain intensity	Efficacy
1 Venipuncture	A = 20 PL = 20	A = 1.5g PL = 1.5g 60 min	NFCS (crying %)	A > PL 21% vs 75% (P<0.001)
2 Venipuncture	A = 2(PL = 1			A > PL 1.7± 1.5 vs 5.7±1 (P<0.01)
3 Heel-stick	A = 30 PL = 29	A = 1.5g PL = 1.5g 60 min	NFCS	A = PL
4 PICC	A = 23 PL = 26	A 1.5 g PL 1.5 g 60 min	PIPP	A = PL

Small sample sizes

Excluded VLBW infants

1. Jain et al., Arch Dis child Fetal Neonatal Ed 2000; 2. Moore et al., J Adv Nurs 2001; 3. Jain et al., Arch Dis child Fetal Neonatal Ed 2001; 4. Ballantyne et al, Adv Neonatal Care 2003

Tetracaine 4% gel Before Venipuncture in Infants (R, PC, DB)*

Lemyre et al., BMC Pediar 2007

	PL (n=71)	Tetracaine (n=71)	P- value
Gestational age (wks)	33 ± 4	33 ± 3.4	NS
Birth weight (kg)	2.1 ± 0.9	2.1 ± 0.9	NS
Sucrose received (n)	58	54	NS
PIPP (1, 2, 3, 4 min)	7.6, 6.5, 8.4, 8.2	7.7, 6.8, 5.9, 5.3	NS
Median duration of cry (s)	5	5	NS
Ease of insertion	2	1	NS
Number of attempts	1	1	NS
Success (%)	36	46	NS

**VLBW 0.5 Š 4.8 Kg; ages 24 Š 41 week GA*

Venipuncture is more than a simple skin puncture

Lemyre et al, BMC Pediatr 2007, Lang et al, Pediatr 1998

- **Restrain**
- **Tourniquet**
- **Handling & immobilization**
  - **Lead to behavioral & physiological reactivity**
- **PIPP; a multidimensional scale**
  - **Infant's response is pain + distress**
- **Conflicting results on efficacy of tetracaine 4%**

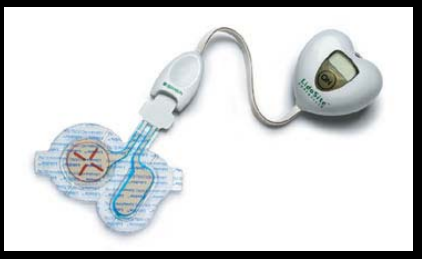
Comparison of EMLA Patch 5% vs. EMLA 5% Cream (RCTs)

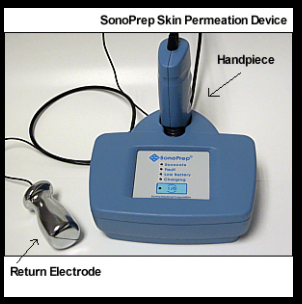
1 .Nilsson et al., Anaesthesia 1994, 2. Chang et al., CJA 1994
3. Robieux et al., Pediatr Res 1992, 4. Calamandrei et al., Reg Anesth 1996

Ref	N (age)	Dose / Duration		Pain intensity	Results
		Patch	Cream		
1	60 (5-15 y)	1g 60-180 min	2.5g 60-180 min	Oucher scale	Cream = patch venipuncture
2	178 (3-10 y)				Cream = patch iv cannulation
3	160 (5-18 y)	1g 60-120 min	1g 60-120 min	VAS	Cream = patch iv cannulation
4	24 (3-16 y)	1g 60-120 min	1g, 60-120 min	VAS, Faces scale	Cream = patch L puncture

Patch has similar efficacy, is more convenient and allows delivery of a smaller predetermined dose

Needle-free Local Anesthetic Delivery Systems





Lidocaine Iontophoresis vs EMLA IV-cannulation (7-16y, R, CO)*

Galinkin et al, Anesth Analg 2002

	Iontophresis (n = 22)	EMLA 5% (n = 22)
Subject reported VAS (0 - 100)	9 (0 - 37)	17 (1 - 51)
Parent reported VAS (0 - 100)	8 (0 - 30)	4 (0 - 16)*
Subject reported distress VAS (0 - 100)	7 (0 - 65)	29 (13 Š 75)
Parent reported distress CHEOP	6 (6 - 8)	6 (6 - 8)
HR (bpm) changes during procedure	12 ± 3	9 ± 2
First attempt success	77%	64%
Satisfaction (1-5 scale)		
-Subject	5 (2 - 5)	5 (2 - 5)
-Parent	5 (3.5 - 5)	4 (2 - 5)
-Observer	5 (2 - 5)	3 (1 Š 5)*
-Technician	5 (1 - 5)*	3 (2 - 4)
Third session; preferred (n)	11	5
No adverse effects except: 2 patients did not tolerate electrical stimulation during iontophoresis		

** 40 mA for a min, lidocaine 2% (20 mg) + epinephrine 1:100,000, EMLA 60 min*
** P < 0.05, Data are median (IQR)*

Low-Dose Lidocaine Iontophoresis System for Topical Anesthesia (RCT)*

Zempsky et al., Clin Ther 2004

	Lidocaine 10%, epinephrine 0.1%	Placebo	P value
N	136	136	
Age (years)	10 ± 3.6	10 ± 3.4	NS
Venipuncture (%)	51.5	52.9	NS
Venous cannulation (%)	44.9	39.7	NS
Patch removal FAS (%)	0.3 ± 0.3	0.3 ± 0.3	NS
Procedural pain (VAS cm)	1.5 ±1.9	2.6 ± 2.3	0.01
FAS pain score- patient	0.36 ± 0.3	0.5 ± 0.3	< 0.001
FAS pain score- parent	0.45 ± 0.3	0.55 ± 0.3	0.02

**Dose 1.7 mA for 10 min (17 mA-min), Lidociane 100 mg with epinephrine1 mg*

Low Dose Lidocaine Iontophoresis System for Topical Anesthesia*

Zempsky et al., Clin Ther 2004

Side Effects	Lidocaine 10%, epinephrine 0.1%	Placebo	P value
Technical failure (n)	5	2	
Erythema at 10 min 24 h	Mild-moderate Mild	Mild-moderate Mild	NS
Edema at 10 min 24 h	Mild None	Mild, None	NS

Discontinuation of iontophoresis in 7:
2 burning sensation
1 vasoconstriction
1 a partial thickness burn from an electrode defect
3 itching &/or urticaria

**Dose 1.7 mA for 10 min; Lidocaine 100 mg, epinephrine1 mg*

A Comparison of a Needle-Free Injection System for lidocaine vs EMLA 5% venous cannulation (RCT)*

Jimenez et al, Anesth & Analg 2006

	J-Tip injector (n = 57)	EMLA (n = 59)	P- value
Age (yr) median (range)	13 (7-19)	14 (10- 19)	NS
Time from application (min)	1.8 ± 0.7	69 ± 32	
No. of			
Ease o			2
No pain during pressure application or occlusive dressing removal (%)	84%	61%	0.004
Cannulation pain; median VAS (range)	0 (0 Š 10)	3 (0 - 10)	0.0001

Faster onset

Less painful during application & venous cannulation

**Buffered Lidocaine 1%, 0.25 mL (2.5 mg)*

Laser-assisted (Er: YAG unit) Anesthesia for Reduction of Venous Cannulation Pain (R, PC, SB)*

Singer et al., Acad Emerg Med 200

		Laser (n=15)	PL (n=15)	P values
Age (years)	0 - 2	3	2	NS
				NS
				NS
White				NS
Hand dorsum				NS
Venous cannu				< 0.05
Successful ca				0.006
Very easy cannulation		67%	47%	NS
Infection/ pigmentation at 1 wk		0	0	NS

Preliminary study in small sample size

CHEOP for < 3 y, Smiley ordinal scale scores for 3-7 y, VAS for > 7 y

Conversion of observational scales and combing it with VAS is controversial

**Energy 3.5 J/ cm^2, one pulse of 600 microseconds over 6 mm diameters. Lidocaine 4% for 5 min*

Conclusion

- Better quality-designed studies are needed to
  - directly compare different modalities of delivery systems in a large number of children particularly the younger age group
  - define the optimal application time
  - PK studies, Cp
    - particularly in infants & for repeated and multiple applications

Thank you for your attention