

Table S1. Paw withdrawal threshold after lidocaine 2.5 % administration

	Time after λ -C delivery (minutes)	L (n=10)		Control group (n=10)		EMLA Group (n=10)		P Value	
		Mean	95% CI	Mean	95 % CI	Mean	95 % CI	L vs Control	L vs EMLA
Cold plate	0	15.333	(4.991-25.675)	7.666	(-2.675-18.009)	3.333	(1.899-4.767)	0.976	0.512
	30	9.000	(-7.289-25.289)	8.333	(3.162-13.504)	4.666	(-5.675-15.009)	0.761	0.403
	60	2.333	(-0.535-5.201)	6.333	(-0.837-13.504)	2.333	(-3.403-8.070)	0.667	0.667
	120	1.000	(-1.484-3.484)	5.666	(-2.318-13.652)	3.000	(-5.956-11.956)	0.901	0.821
	180	1.000	(-1.484-3.484)	5.000	(0.697-9.302)	2.666	(-4.922-10.255)	0.333	0.546
	240	0.333	(-1.100-1.767)	1.666	(-1.201-4.535)	2.000	(-0.484-4.484)	0.000	0.333
Hot plate	0	4.900	(4.242-5.557)	4.133	(1.477-6.789)	7.033	(4.377-9.689)	0.575	0.758
	30	3.600	(2.854-4.345)	3.733	(-1.371-8.838)	2.533	(2.389-2.676)	0.953	0.333
	60	4.433	(1.239-7.627)	5.133	(2.620-7.646)	5.633	(1.257-10.009)	0.536	0.748
	120	4.966	(2.219-7.714)	2.933	(0.625-5.241)	4.233	(0.496-7.970)	0.198	0.782
	180	4.600	(2.861-6.338)	3.533	(2.307-4.758)	2.766	(2.049-3.483)	0.027	0.758
	240	3.866	(2.498-5.234)	3.066	(2.779-3.353)	2.833	(2.116-3.550)	0.300	0.967
Algesimeter	0	6.500	(2.021-10.978)	10.666	(-0.874-22.207)	16.166	(2.88-29.447)	0.110	0.391
	30	4.333	(3.616-5.050)	12.666	(0.412-24.920)	17.000	(-0.210-34.210)	0.731	0.000
	60	6.166	(1.464-10.869)	14.833	(-7.707-37.373)	18.000	(-2.894-38.894)	0.645	0.716
	120	4.333	(2.436-6.230)	3.666	(-1.353-8.686)	16.500	(-1.542-34.542)	0.212	0.750
	180	5.166	(2.581-7.752)	8.400	(2.55-14.241)	9.500	(3.808-15.191)	0.869	0.367
	240	6.333	(-3.782-16.449)	9.033	(1.41-16.650)	14.833	(-7.707-37.373)	0.547	0.027

λ -C: λ -carrageenan; L: Lidocaine 2.5 %; EMLA: Eutectic Mixture of Local Anesthetics; CI: confidence interval

Table S2. Paw withdrawal threshold after lidocaine-cyclodextrin 2.5% administration

	Time after λ -C delivery (minutes)	L-CD (n=10)		Control group (n=10)		EMLA Group (n=10)		P Value	
		Mean	95% CI	Mean	95 % CI	Mean	95 % CI	L-CD vs Control	L-CD vs EMLA
Cold plate	0	12.033	(11.889-12.176)	7.666	(-2.675-18.009)	3.333	(1.899-4.767)	0.512	0.000
	30	13.000	(-9.079-35.079)	8.333	(3.162-13.504)	4.666	(-5.675-15.009)	0.299	0.657
	60	7.000	(-10.389-24.389)	6.333	(-0.837-13.504)	2.333	(-3.403-8.070)	0.333	0.333
	120	7.000	(-2.936-16.936)	5.666	(-2.318-13.652)	3.000	(-5.956-11.956)	0.234	0.512
	180	6.000	(-4.828-16.828)	5.000	(0.697-9.302)	2.666	(-4.922-10.255)	0.073	0.285
	240	4.000	(-5.936-13.936)	1.666	(-1.201-4.535)	2.000	(-0.484-4.484)	1	0.667
Hot plate	0	4.266	(2.402-6.131)	4.133	(1.477-6.789)	7.033	(4.377-9.689)	0.946	0.763
	30	3.233	(0.846-5.620)	3.733	(-1.371-8.838)	2.533	(2.389-2.676)	0.476	0.237
	60	2.300	(1.554-3.045)	5.133	(2.620-7.646)	5.633	(1.257-10.009)	0.365	0.351
	120	2.300	(1.217-3.382)	2.933	(0.625-5.241)	4.233	(0.496-7.970)	0.662	0.358
	180	2.266	(1.749-2.783)	3.533	(2.307-4.758)	2.766	(2.049-3.483)	0.577	0.154
	240	3.600	(2.109-5.090)	3.066	(2.779-3.353)	2.833	(2.116-3.550)	0.333	1
Algesimeter	0	13.100	(-5.823-32.023)	10.666	(-0.874-22.207)	16.166	(2.88-29.447)	0.888	0.831
	30	8.666	(-0.488-17.822)	12.666	(0.412-24.920)	17.000	(-0.210-34.210)	0.862	0.130
	60	6.133	(3.138-9.128)	14.833	(-7.707-37.373)	18.000	(-2.894-38.894)	0.167	0.806
	120	12.500	(5.927-19.072)	3.666	(-1.353-8.686)	16.500	(-1.542-34.542)	0.121	0.917
	180	11.566	(9.735-13.397)	8.400	(2.55-14.241)	9.500	(3.808-15.191)	0.440	0.324
	240	10.666	(3.388-17.944)	9.033	(1.41-16.650)	14.833	(-7.707-37.373)	0.068	0.452

λ -C: λ -carrageenan; L-CD: lidocaine-cyclodextrin 2.5%; EMLA: Eutectic Mixture of Local Anesthetics;
CI: confidence interval

Table S3. Paw withdrawal threshold after lidocaine – chitosan 4 % administration

	Time after λ -C delivery (minutes)	L-CS (n=10)		Control group (n=10)		EMLA Group (n=10)		P Value	
		Mean	95% CI	Mean	95 % CI	Mean	95 % CI	L-CS vs Control	L-CS vs EMLA
Cold plate	0	12.666	(-1.889-27.222)	7.666	(-2.675-18.009)	3.333	(1.899-4.767)	0.403	0.109
	30	13.333	(3.293-23.372)	8.333	(3.162-13.504)	4.666	(-5.675-15.009)	0.754	0.396
	60	3.333	(-1.837-8.504)	6.333	(-0.837-13.504)	2.333	(-3.403-8.070)	0.821	0.821
	120	1.000	(-1.484-3.484)	5.666	(-2.318-13.652)	3.000	(-5.956-11.956)	0.901	0.821
	180	3.000	(-3.572-9.572)	5.000	(0.697-9.302)	2.666	(-4.922-10.255)	0.121	0.091
	240	2.333	(-1.461-6.127)	1.666	(-1.201-4.535)	2.000	(-0.484-4.484)	0.454	0.121
Hot plate	0	3.833	(3.034-4.631)	4.133	(1.477-6.789)	7.033	(4.377-9.689)	0.537	0.355
	30	3.600	(3.169-4.030)	3.733	(-1.371-8.838)	2.533	(2.389-2.676)	0.713	0.000
	60	3.833	(3.316-4.350)	5.133	(2.620-7.646)	5.633	(1.257-10.009)	0.196	0.530
	120	4.133	(3.099-5.167)	2.933	(0.625-5.241)	4.233	(0.496-7.970)	0.890	0.130
	180	4.200	(1.219-7.181)	3.533	(2.307-4.758)	2.766	(2.049-3.483)	0.398	0.333
	240	4.333	(0.942-7.724)	3.066	(2.779-3.353)	2.833	(2.116-3.550)	0.428	0.905
Algesimeter	0	13.833	(-10.261-37.928)	10.666	(-0.874-22.207)	16.166	(2.88-29.447)	0.118	0.163
	30	14.500	(-1.357-30.357)	12.666	(0.412-24.920)	17.000	(-0.210-34.210)	0.399	0.870
	60	17.000	(-7.465-41.465)	14.833	(-7.707-37.373)	18.000	(-2.894-38.894)	0.936	0.297
	120	10.166	(-11.069-31.403)	3.666	(-1.353-8.686)	16.500	(-1.542-34.542)	0.611	0.351
	180	7.000	(5.757-8.242)	8.400	(2.55-14.241)	9.500	(3.808-15.191)	0.690	0.546
	240	5.333	(3.436-7.230)	9.033	(1.41-16.650)	14.833	(-7.707-37.373)	0.837	0.318

λ -C: λ -carrageenan; L-CS: lidocaine – chitosan 4 %; EMLA: Eutectic Mixture of Local Anesthetics; CI: confidence interval

Table S4. Paw withdrawal threshold after lidocaine - chitosan hydrochloride administration

	Time after λ -C delivery (minutes)	L-CSH (n=10)		Control group (n=10)		EMLA Group (n=10)		P Value	
		Mean	95% CI	Mean	95 % CI	Mean	95 % CI	L-CSH vs Control	L-CSH vs EMLA
Cold plate	0	8.000	(1.427-14.572)	7.666	(-2.675-18.009)	3.333	(1.899-4.767)	0.700	0.788
	30	7.333	(1.596-13.070)	8.333	(3.162-13.504)	4.666	(-5.675-15.009)	0.821	0.821
	60	7.333	(-8.829-23.496)	6.333	(-0.837-13.504)	2.333	(-3.403-8.070)	0.305	0.305
	120	6.666	(-5.072-18.406)	5.666	(-2.318-13.652)	3.000	(-5.956-11.956)	0.235	0.043
	180	4.333	(-10.222-18.889)	5.000	(0.697-9.302)	2.666	(-4.922-10.255)	0.109	0.103
	240	1.333	(-2.461-5.127)	1.666	(-1.201-4.535)	2.000	(-0.484-4.484)	0.879	0.788
Hot plate	0	5.066	(0.804-9.328)	4.133	(1.477-6.789)	7.033	(4.377-9.689)	0.277	0.460
	30	4.700	(2.961-6.438)	3.733	(-1.371-8.838)	2.533	(2.389-2.676)	0.622	0.091
	60	8.133	(-4.308-20.574)	5.133	(2.620-7.646)	5.633	(1.257-10.009)	0.570	0.146
	120	4.900	(0.299-9.500)	2.933	(0.625-5.241)	4.233	(0.496-7.970)	0.235	0.745
	180	4.466	(3.462-5.470)	3.533	(2.307-4.758)	2.766	(2.049-3.483)	0.177	0.909
	240	5.033	(1.134-8.932)	3.066	(2.779-3.353)	2.833	(2.116-3.550)	0.523	0.810
Algesimeter	0	11.166	(-13.341-35.674)	10.666	(-0.874-22.207)	16.166	(2.88-29.447)	0.663	0.944
	30	8.166	(1.792-14.540)	12.666	(0.412-24.920)	17.000	(-0.210-34.210)	0.542	0.189
	60	13.833	(-4.603-32.270)	14.833	(-7.707-37.373)	18.000	(-2.894-38.894)	0.365	0.996
	120	15.833	(-4.360-36.027)	3.666	(-1.353-8.686)	16.500	(-1.542-34.542)	0.805	0.233
	180	11.833	(-1.21-24.880)	8.400	(2.55-14.241)	9.500	(3.808-15.191)	0.661	0.104
	240	15.000	(0.675-29.324)	9.033	(1.41-16.650)	14.833	(-7.707-37.373)	0.764	0.245

λ -C: λ -carrageenan; L-CSH: lidocaine - chitosan hydrochloride; EMLA: Eutectic Mixture of Local Anesthetics; CI: confidence interval

Table S5. Paw withdrawal threshold after lidocaine-chitosan-liposomes administration

	Time after λ -C delivery (minutes)	L-CS-LP (n=10)		Control group (n=10)		EMLA Group (n=10)		P Value	
		Mean	95% CI	Mean	95 % CI	Mean	95 % CI	L-CS-LP vs Control	L-CS-LP vs EMLA
Cold plate	0	14.000	(11.515-16.484)	7.666	(-2.675-18.009)	3.333	(1.899-4.767)	0.179	0.333
	30	8.666	(1.077-16.255)	8.333	(3.162-13.504)	4.666	(-5.675-15.009)	0.300	0.058
	60	6.000	(-0.572-12.572)	6.333	(-0.837-13.504)	2.333	(-3.403-8.070)	0.788	0.788
	120	2.333	(-1.461-6.127)	5.666	(-2.318-13.652)	3.000	(-5.956-11.956)	0.780	0.942
	180	2.333	(-1.461-6.127)	5.000	(0.697-9.302)	2.666	(-4.922-10.255)	0.879	0.667
	240	1.666	(0.232-3.100)	1.666	(-1.201-4.535)	2.000	(-0.484-4.484)	0.000	0.333
Hot plate	0	5.766	(3.758-7.774)	4.133	(1.477-6.789)	7.033	(4.377-9.689)	0.272	0.454
	30	5.233	(-1.003-11.470)	3.733	(-1.371-8.838)	2.533	(2.389-2.676)	0.988	0.275
	60	4.366	(4.079-4.653)	5.133	(2.620-7.646)	5.633	(1.257-10.009)	0.698	0.018
	120	4.633	(1.429-7.837)	2.933	(0.625-5.241)	4.233	(0.496-7.970)	0.910	0.109
	180	4.233	(2.865-5.601)	3.533	(2.307-4.758)	2.766	(2.049-3.483)	0.235	0.967
	240	5.566	(2.139-8.993)	3.066	(2.779-3.353)	2.833	(2.116-3.550)	0.116	0.551
Algesimeter	0	6.000	(2.273-9.726)	10.666	(-0.874-22.207)	16.166	(2.88-29.447)	0.402	0.121
	30	5.500	(1.021-9.978)	12.666	(0.412-24.920)	17.000	(-0.210-34.210)	0.244	0.488
	60	4.600	(-0.386-9.586)	14.833	(-7.707-37.373)	18.000	(-2.894-38.894)	0.693	0.054
	120	8.500	(5.213-11.786)	3.666	(-1.353-8.686)	16.500	(-1.542-34.542)	0.121	0.917
	180	7.166	(1.995-12.337)	8.400	(2.55-14.241)	9.500	(3.808-15.191)	0.569	0.667
	240	7.166	(1.995-12.337)	9.033	(1.41-16.650)	14.833	(-7.707-37.373)	0.863	0.618

λ -C: λ -carrageenan; L-CS-LP: lidocaine-chitosan-liposomes; EMLA: Eutectic Mixture of Local Anesthetics; CI: confidence interval

Table S6. Statistical indicators for the researched substances

Time (min.)	Cold Plate						Hot Plate					
	0	30	60	120	180	240	0	30	60	120	180	240
Lidocaine - Chitosan Hydrochloride												
<i>Min</i>	6.0	6.0	1.0	3.0	0.0	0.0	3.5	4.2	4.3	3.1	4.1	3.8
<i>Max</i>	11.0	10.0	14.0	12.0	11.0	3.0	6.9	5.5	13.8	6.8	4.9	6.8
<i>SD</i>	2.64	2.30	6.50	4.72	5.85	1.52	1.71	0.70	5.00	1.85	0.40	1.56
Control												
<i>Min</i>	3.00	6.00	3.00	2.0	4.00	1.00	2.90	2.40	4.50	2.30	3.20	3.00
<i>Max</i>	11.0	10.0	8.00	8.0	7.00	3.00	4.80	6.10	6.30	4.00	4.10	3.20
<i>SD</i>	4.16	2.08	2.88	3.21	1.73	1.15	1.06	2.05	1.01	0.92	0.49	0.11
EMLA™												
<i>Min</i>	3.00	0.00	1.00	0.00	0.00	1.00	6.10	2.50	3.60	2.80	2.60	2.50
<i>Max</i>	4.00	8.00	5.00	7.00	6.00	3.00	8.20	2.60	6.70	5.80	3.10	3.00
<i>SD</i>	0.57	4.16	2.30	3.60	3.05	1.00	1.06	0.05	1.76	1.50	0.28	0.28
Lidocaine - Cyclodextrin 2.5%												
<i>Min</i>	12.0	3.00	0.00	3.00	3.00	0.00	3.50	2.20	2.00	1.80	2.10	3.00
<i>Max</i>	12.1	20.0	14.0	11.0	11.0	8.00	5.00	4.10	2.60	2.60	2.50	4.20
<i>SD</i>	0.05	8.88	7.00	4.00	4.35	4.00	0.75	0.96	0.30	0.43	0.20	0.60
Lidocaine - Chitosan 4%												
<i>Min</i>	6.00	9.00	1.00	0.00	0.00	1.00	3.60	3.50	3.60	3.80	3.00	3.10
<i>Max</i>	17.0	17.0	5.00	2.00	5.00	4.00	4.20	3.80	4.00	4.60	5.40	5.80
<i>SD</i>	5.85	4.04	2.08	1.00	2.64	1.52	0.32	0.17	0.20	0.41	1.20	1.36
Lidocaine - Chitosan - Liposomes												
<i>Min</i>	13.0	6.00	3.00	1.00	1.00	1.00	4.90	2.60	4.30	3.20	3.70	4.00
<i>Max</i>	15.0	12.0	8.00	4.00	4.00	2.00	6.50	7.60	4.50	5.70	4.80	6.60
<i>SD</i>	1.00	3.05	2.64	1.52	1.52	0.57	0.80	2.51	0.11	1.28	0.55	1.37
Lidocaine – Liposomes 1.7%												
<i>Min</i>	6.00	2.00	3.00	0.00	0.00	0.00	5.20	2.80	3.70	3.70	3.40	3.30
<i>Max</i>	13.0	10.0	4.00	6.00	2.00	1.00	6.30	4.40	4.70	6.80	6.50	6.50
<i>SD</i>	3.60	4.16	0.57	3.21	1.15	0.57	0.60	0.89	0.51	1.55	1.59	1.61
Lidocaine												
<i>Min</i>	12.0	3.00	1.00	0.00	0.00	0.00	4.70	3.30	3.50	3.80	3.80	3.30
<i>Max</i>	20.0	16.0	3.00	2.00	2.00	1.00	5.20	3.90	5.90	6.00	5.10	4.40
<i>SD</i>	4.16	6.55	1.15	1.00	1.00	0.57	0.26	0.30	1.28	1.10	0.70	0.55

Table S7. Statistical indicators for the researched substances

Algesimeter						
Time (min.)	0	30	60	120	180	240
Lidocaine - Chitosan Hydrochloride						
<i>Min</i>	4.5	6.0	7.5	9.5	6.5	10.5
<i>Max</i>	22.5	11.0	22.0	25.0	17.0	21.5
<i>SD</i>	9.86	2.56	7.42	8.12	5.25	5.76
Control						
<i>Min</i>	7.50	7.00	4.5	2.5	6.0	5.50
<i>Max</i>	16.0	16.0	21.5	6.0	10.7	11.0
<i>SD</i>	4.64	4.93	0.07	2.02	2.35	3.06
EMLA™						
<i>Min</i>	11.5	13.0	8.50	9.0	7.50	4.50
<i>Max</i>	22.0	25.0	24.5	23.5	12.0	21.5
<i>SD</i>	5.34	6.92	8.41	7.26	2.29	9.07
Lidocaine - Cyclodextrin 2.5%						
<i>Min</i>	5.80	4.50	5.00	10.5	11.0	8.50
<i>Max</i>	21.0	11.5	7.40	15.5	12.4	14.0
<i>SD</i>	7.61	3.68	1.20	2.64	0.73	2.92
Lidocaine - Chitosan 4%						
<i>Min</i>	7.50	7.50	6.00	4.50	6.50	4.50
<i>Max</i>	25.0	20.0	25.0	20.0	7.50	6.00
<i>SD</i>	9.69	6.38	9.84	8.54	0.50	0.76
Lidocaine - Chitosan - Liposomes						
<i>Min</i>	4.50	4.00	2.30	7.00	5.00	5.50
<i>Max</i>	7.50	7.50	6.00	9.50	6.50	9.50
<i>SD</i>	1.50	1.80	2.00	1.32	0.76	2.08
Lidocaine – Liposomes 1.7%						
<i>Min</i>	6.00	5.00	5.50	4.00	8.50	5.50
<i>Max</i>	10.5	14.0	12.5	10.5	12.5	13.5
<i>SD</i>	2.36	4.93	3.54	3.32	2.17	4.16
Lidocaine						
<i>Min</i>	5.00	4.00	4.00	3.50	4.00	3.50
<i>Max</i>	8.50	4.50	7.50	5.00	6.00	11.0
<i>SD</i>	1.80	0.28	1.89	0.76	1.04	4.07