Original Article

Gentle Human Touch (GHT) may Potentiate the Analgesic Efficacy of Topical Anesthetic and other Non-Pharmacological Measures during Retinopathy of Prematurity Screening: A Prospective Study

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Abstract

Background: There is a global increase in the incidence of retinopathy of prematurity (ROP). As the most common cause of childhood blindness, a routine screening protocol was established for preterm neonates, in which unfortunately, the screening process involves several painful interventions.

Aim of work: Comparing the analgesic efficacy of oral 10% dextrose, breast milk, and sterile water with or without gentle human touch (GHT) during retinopathy of prematurity (ROP) screening.

Patients and methods: 90 preterms undergoing ROP screening were divided into groups: EBM (n = 30) (GI), 10% dextrose (n = 30)(GII) or sterile water (n = 30) (GIII), a minute before examination. Premature infant pain profile (PIPP) was assessed before and after GHT.

Results: Saturation was statistically significant between GI and GIII (P=0.000) and between GII and GIII (P=0.025) before GHT. After GHT Peak heart rate and increase in heart rate from baseline were statistically significant between G(I) and G(III) (P=0.000), between G(I) and G(II) regarding increase in heart rate (P=0.000) and between G(II)and (III) regarding peak heart rate (P=0.019). Mean PIPP was significant for individual group (P = 0.000) before and after GHT.

Conclusions: GHT and a topical anesthetic potentiate the analgesic efficacy of non-pharmacological measures during retinopathy of prematurity (ROP) screening.

Key words: PIPP, Premature Infant Pain Profile, Gentle human touch, GHT, 10% dextrose, ROP, EBM

Introduction

Recurrent painful episodes caused by repeated invasive interventions induce an exaggerated stress response in neonates [1]. In addition, it causes remodeling of the spinal neurons, thereby increasing sensitization of their nervous system. This, in turn, interferes with the developing central nervous system and results in chronic pain, discomfort, and growth delay [2]. The long-term effects include behavioral, emotional, and learning deficits [3].

There is a global increase in the incidence of retinopathy of prematurity (ROP) [4]. As the most common cause of childhood blindness, a routine screening protocol was established for preterm neonates [5]. Unfortunately, the screening process involves several painful interventions, including the use of mydriatics and a speculum, as well as the contact of a RetCam device on their eyes, or the brightness of either an indirect ophthalmoscope or RetCam [6]. Therefore, trials aiming at relieving pain and discomfort are still mandatory during screening.

Several pharmacological and non-pharmacological strategies have been used to alleviate the pain experienced by preterm neonates [7]. To date, these strategies have not been found convenient for reducing their pain response. Accordingly, more studies are needed to determine an effective strategy in this regard [5, 6, 8].

Several studies proved the analgesic efficacy of either oral dextrose, expressed breast milk (EBM) [9], or nonnutritive sucking [10]. Only, a few studies included several combinations including touch [8]. Touch sensation is a cornerstone of interactions; it is the most rapidly developing sense in infancy and the most important for sensory and cognitive development [11-13]. Unfortunately, it is the most under-diagnosed analgesic procedure in the NICU [14]. Accordingly, this research was conducted to study the analgesic efficacy of human milk, 10% dextrose,

and distilled water as a placebo, on its own or combined with gentle human touch (GHT) as an adjuvant to a topical anesthetic during screening for ROP.

Methods

Ninety neonates indicated for ROP screening (less than or equal to 32 weeks old and weighing less than or equal to 1,500 g) were included in this study in the period between May 1, 2019, and February 28, 2021.

In addition, These neonates were equally divided and included for screening at Cairo University Children Hospital (Abourreesh El Mounira, Egypt) using the RetCam Shuttle imaging system. Mydriatics, 0.2% cyclopentolate, and 0.1% phenylephrine were administered 30 minutes before screening. Topical anesthetic eye drops, benoxinate hydrochloride, and a speculum were used. The screening was performed by an experienced neonatologist as recommended by the American Academy of Pediatrics (15) and classified according to the Revised International Classification of Retinopathy of Prematurity (16). Neonates weighing less than 1,250 g received 2 ml of either 10% glucose, sterile water, or EBM, and those weighing more than or equal to 1,250 g received 5 ml of either 10% glucose, sterile water, or EBM. Neonates were also swaddled and nested during the screening of the right eye, and the same was done with the left eye 30 minutes after finishing with the right, in addition to gentle human touch (GHT). If ROP was diagnosed, an ophthalmologist from the ROP team confirmed the diagnosis, staging, and the need for intervention. All findings were documented and recorded. The quantification of pain was done using the premature infant pain profile (PIPP) score[17], which included a summation of seven items, i.e., gestational age, an increase in heart rate, a decrease in oxygen saturation, arousal state, and expressions of pain; (eyebrow furrowing, nasolabial fold, eye squeezing). Each item was scored ranging from 0–3; the maximum possible

score was 21. Higher scores denoted more severe pain. To schedule PIPP score, the right eye was standardized for assessment of the score before the application of GHT, and the left eye was standardized for assessment afterward. The baseline heart rate and oxygen saturation were documented before RetCam screening, and continuous measuring of the heart rate were recorded. The highest heart rate and oxygen saturation after one minute was included and recorded by a well-experienced nurse. Facial expressions were recorded before, during, and 1 minute after the end of the exam. The grading of the nasolabial furrow, eye squeeze, and eyebrow furrow for each exam was completed according to the PIPP scale. All of the measurements were documented.

Gentle human touch: A protocol for GHT was applied upon examination of the left eye, 30 minutes after examination of the right eye [18], and lasted for 10 minutes; this involved placement of the right fingertips tangential with the left neonatal eyebrow and with the palm touching the neonatal crown. The left thumb was placed on the middle of the left shoulder with the left hand on the infant's upper arm

Exclusion criteria: Neonates who were excluded from the study included those on nothing per orum, who had congenital malformations, who were ventilated, who were receiving oral or intravenous analgesics, and those who received anticonvulsants.

Ethical approval

The study design conformed to the Revised Declaration of Helsinki and was approved by the Scientific Ethics Committee of the Pediatric Department of the Faculty of Medicine, Cairo University. Informed written consent was obtained from the parents of the patients for their inclusion in the study.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (IBM SPSS, v.23). The mean, standard deviation, and

range represented quantitative data when parametric. The median and interquartile range represented non-parametric data. Numbers and percentages represented qualitative variables.

A chi-square test or a Fisher's exact test (or both) were used to compare qualitative data when the expected count was less than five in any cell.

Paired groups with quantitative data and parametric distribution were compared using a paired t-test, while a Wilcoxon signed-rank test was used to compare data with a non-parametric distribution.

A one-way ANOVA test, followed by post hoc analysis using an LSD test, was used to compare more than two groups with quantitative data and parametric distribution, while a Kruskal–Wallis test was used in cases of non-parametric distribution.

The confidence interval was set to 95% with a 5% accepted margin of error. The P-value was considered significant as follows:

$P \geq 0.05$: Nonsignificant (NS)

$P < 0.05$: Significant (S)

$P < 0.01$: Highly significant (HS).

Results

A total of 90 preterm neonates were enrolled in the current research during the study period and divided into three groups. Group I (GI) included 30 neonates who received EBM, Group II (GII) included 30 neonates who received 10% dextrose, and Group III (G III) included neonates who received distilled water. Table (1) shows no statistical significance regarding gestational age, birth weight, weight at screening, and sex between the studied groups. Table (2) shows the physiological indicators for the PIPP score before GHT. One minute after the exam, oxygen saturation was lowest for G III (distilled water), and this difference was highly significant, as shown in Table (2) Infants given EBM had the highest oxygen saturation one minute after the exam. This difference was highly significant when compared to infants who were given distilled water in G III (P = 0.000). There was also a

statistically significant difference between infants who were given EBM and those given 10% dextrose (P = 0.025). Quantitative summation of PIPP, together with the individual facial, physiological, and behavioral parameters, shows no statistical significance between all three groups before gentle human touch, as shown in Table (3). After GHT, infants who were given distilled water had the highest heart rate and the highest increase in heart rate from the baseline with highly significant results compared to GI (P = 0.000); there was also a statistical significance compared with GII regarding peak heart rate (P = 0.019), as shown in Table(4). An increase in heart rate was highly significant when GI was compared to GII (P = 0.000), as shown in Table (4). Individual physiological, behavioral, and facial parameters, together with a quantitative summation of PIPP, showed no statistical significance between all groups after GHT was applied, as shown in Table (5). There was a highly significant difference between the PIPP in GI before and after GHT (P = 0.000) concerning peak heart rate, an increase in heart rate from the baseline, heart rate and oxygen saturation one minute after the exam, behavioral state, and the mean PIPP. There was also a highly significant difference before as compared to after GHT regarding the lowest saturation during the exam (P = 0.004), brow bulge (P = 0.001), and heart rate (P = 0.001), as shown in Table (6). There was a highly significant difference between the PIPP in GII before and after GHT (P = 0.000) concerning peak heart rate, an increase in heart rate from the baseline, heart rate one minute after the exam, lowest saturation during the exam, behavioral state, heart rate score, and the mean PIPP score. There was also a significant difference before compared to after GHT concerning baseline heart, baseline saturation, saturation one minute after the exam, and difference in saturation with P values equal to 0.025, 0.013, 0.023, and 0.014 respectively, as shown in Table (7). There was a highly

significant difference between the PIPP in GIII before and after GHT (P = 0.000) in terms of peak heart rate, an increase in heart rate from the baseline, heart rate one minute after the exam, difference in saturation, behavioral state and mean PIPP. There was also a highly significant difference between baseline saturation, the lowest saturation, and heart rate score with P values of 0.003, 0.001, and 0.001 respectively, and a significant difference between baseline heart rate with a P value of 0.025 as shown in Table(8).

Discussion

The global incidence of ROP is constantly rising. Despite using topical anesthetics, the screening process is painful, owing to the use of a speculum, indentor, the RetCam device, and indirect ophthalmoscopy with the glaring effect of both [19]. Mukherjee et al., 2006 [20] stated that physiological parameters using the RetCam were better compared with indirect ophthalmoscope examination due to the absence of an indentor. Thus, RetCam screening may

be less painful, and this particular device is always used for screening at our center.

The commonly used analgesics for neonatal pain include 10% dextrose orally, which is safe and readily available [20, 21]. Breastmilk was found to have an analgesic effect, owing to the presence of lactose and tryptophan. Tryptophan is a precursor of melatonin, which increases beta-endorphins levels, a mechanism by which breast milk exerts its nociceptive effect [22, 23].

In our study, comparing the three groups who received EBM (GI), D10% (GII), and distilled water (GIII) before GHT, there was no statistical significance in the mean PIPP scores between the preterm neonates conducted in GI or GII. This was in accordance with a research by Riberio et al., 2013 [24], Taplak and Erdem 2017 [25], and Nayak et al., [9]. Although there was a highly significant difference between EBM (GI) and sterile water (GIII), this result was supported by that of Rosali et,al., 2015 [26] and a

significant difference between GII and GIII this finding was in accordance with a research by Tablak and Erdem., 2017[25], and Boyle et al., 2006 [27] but against Gal et al.,2005 [28] and Grabska et al.,2005 [29]. However, the neonates in all three groups still experienced moderate pain, based on the PIPP scale.

When GHT was attempted, no difference was observed between the three groups. However, when comparing individual groups before and after human touch intervention, there was a dramatic decrease in the PIPP score in all groups. This was supported by a research conducted by Sun et al., 2010[8] where GHT showed a dramatic decrease in; peak heart rate, increase of heart rate from the base line and 1 minute after the exam. There was also a dramatic increase in both the lowest saturation during the exam and 1 minute after the exam in all groups. The final result was a dramatic decrease in the mean PIPP scores in all groups. Gentle human touch affected the physiological responses in all of the

groups and, to a lesser extent, the behavioral and facial parameters in GI, and only the behavioral parameters in GIII. Neither the behavioral nor the facial parameters were affected in GII. However, the pain was still perceived as moderate before human touch or after the mean PIPP scores decreased.

According to an existing meta-analysis [9, 30], there should be a topical anesthetic, sweet taste, and an adjuvant to ameliorate pain. However, no specific combination of treatments could mask the severe pain of lid retraction or scleral depression if an ophthalmoscope was used. Senkowsi [31] concluded that multisensory stimulation had a long-lasting effect on pain reduction. Hence, a combination of GHT and non-pharmacological analgesia, in addition to topical anesthesia, was attempted. This combination stimulated various sensory nerve endings and reduced pain from various circuits. This may have been due to competition between painful and non-painful stimuli [31] or as a result of

distracting a newborn, thereby preventing the transmission of pain to the cerebral cortex, as noted by Sun et al., 2010[8] In addition, GHT was found to decrease cortisol levels. [32].

Our study showed that there is no difference between the three groups when compared altogether after human touch. This may indicate that Gentle human touch effect may even exceed the individual effect exerted by EBM or 10% dextrose and reaching the same level with sterile water only though, this finding needs more studies to prove or de prove it.

The limitation in our study was the relatively small number of patients and the obligation to perform gentle human touch in the same setting, only thirty minutes after finishing with the right eye which may have exhausted our preterms and accordingly intervened with the final results of the PIPP score. Unfortunately, we had no other alternative owing to the incompliance of our patients in the first place and the need to fix all other demographic data to allow for a reliable comparison.

Conclusions

To sum up, GHT when added to a topical anesthetic and; EBM, dextrose 10% or distilled water decreases the mean PIPP scores in all groups and should be tried safely to ameliorate pain of ROP screening but further studies are needed to abate the pain totally.

Author's contributions

NG: Data collection, acquisition, design of the study, interpretation of data, drafting, writing, revising, finally approving the manuscript for submission and publication. SE: Data collection, interpretation of data, drafting, writing, revising, finally approving the manuscript for submission and publication

Conflict of interest

The authors declare that they have no competing interests

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Table (1): Demographic Data

Item		Group I No. = 30	Group II No. = 30	Group III No. = 30	Test value	P-value	Sig.
Gestational age (weeks)	Mean ± SD	30.63 ± 1.22	30.63 ± 0.93	31.10 ± 0.92	2.045•	0.136	NS
	Range	28 – 32	28 – 32	29 – 32			
Corrected GA	Mean ± SD	34.63 ± 1.22	34.63 ± 0.93	35.10 ± 0.92	2.045•	0.136	NS
	Range	32 – 36	32 – 36	33 – 36			
Sex	Male	16 (53.3%)	15 (50.0%)	15 (50.0%)	0.089*	0.957	NS
	Female	14 (46.7%)	15 (50.0%)	15 (50.0%)			
Birth weight(gms)	Mean ± SD	1170.34 ± 163.69	1326.17 ± 198.50	1383.33 ± 162.13	1.873•	0.162	NS
	Range	1015 – 1400	900 – 1420	1000 – 1390			
Weight \at screening(gms)	Mean ± SD	1420.67 ± 190.84	1326.17 ± 198.50	1383.33 ± 162.13	1.997•	0.142	NS
	Range	1020 – 1880	950 – 1800	1100 – 1700			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

*: Chi-square test; •: One Way ANOVA test

Table (2)Physiological indicators of the PIPP before gentle human touch:

		Group I No. = 30	Group II No. = 30	Group III No. = 30	Test value	P-value	Sig.
Baseline heart rate	Mean ± SD	131.77 ± 12.73	128.90 ± 13.41	136.40 ± 14.24	2.366•	0.100	NS
	Range	108 – 160	108 – 152	108 – 160			
Peak heart rate	Mean ± SD	173.60 ± 16.92	174.17 ± 17.86	181.67 ± 10.55	2.547•	0.084	NS
	Range	128 – 200	127 – 200	160 – 200			
Increase in heart rate from baseline	Mean ± SD	41.43 ± 15.18	45.10 ± 17.64	45.27 ± 11.52	0.626•	0.537	NS
	Range	17 – 62	14 – 71	25 – 72			
Heart rate 1 min post exam	Mean ± SD	152.97 ± 13.62	156.47 ± 15.33	161.07 ± 9.96	2.857•	0.063	NS
	Range	120 – 174	118 – 182	142 – 177			
Baseline saturation	Mean ± SD	97.83 ± 2.34	97.33 ± 2.48	97.03 ± 2.19	0.896•	0.412	NS
	Range	93 – 100	92 – 100	93 – 100			
Lowest saturation during exam	Mean ± SD	91.07 ± 2.86	90.17 ± 2.77	90.27 ± 2.56	0.977•	0.380	NS
	Range	85 – 95	85 – 95	86 – 94			
Oxygen Saturation 1min after exam	Mean ± SD	96.70 ± 3.14	95.23 ± 3.04	93.37 ± 3.31	8.367•	0.000	HS
	Range	90 – 100	88 – 100	88 – 99			
Difference in saturation	Mean ± SD	6.83 ± 1.32	7.13 ± 1.38	6.77 ± 1.07	0.716	0.491	NS
	Range	5 – 10	5 – 9	5 – 10			
Post hoc analysis							
		Group I Vs group II	Group I Vs group III	Group II Vs group III			
Oxygen Saturation 1min after exam (1)		0.076 (NS)	0.000 (HS)	0.025 (S)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: One Way ANOVA test

Table (3) Individual behavioral physiological and facial parameters and mean PIPP before gentle human touch

Item		Group I No. = 30	Group II No. = 30	Group III No. = 30	Test value	P-value	Sig.
GA Score	Median (IQR)	1 (0 – 1)	1 (1 – 1)	1 (0 – 1)	2.825≠	0.243	NS
	Range	0 – 1	0 – 1	0 – 1			
Behavioral state	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	1.215≠	0.545	NS
	Range	2 – 3	2 – 3	2 – 3			
Brow bulge	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.101≠	0.951	NS
	Range	2 – 3	2 – 3	2 – 3			
Nasolabial furrow	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	1.308≠	0.520	NS
	Range	2 – 3	2 – 3	2 – 3			
Eye squeeze	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	1.496≠	0.473	NS
	Range	2 – 3	2 – 3	2 – 3			
PIPP HR	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.107≠	0.948	NS
	Range	2 – 3	2 – 3	2 – 3			
PIPP saturation	Median (IQR)	2 (2 – 2)	2 (2 – 2)	2 (2 – 2)	0.558≠	0.756	NS
	Range	1 – 3	1 – 3	1 – 3			
Mean PIPP Score	Median (IQR)	16 (15 – 17)	16 (15 – 17)	16 (15 – 17)	0.120≠	0.942	NS
	Range	14 – 19	14 – 19	13 – 19			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

≠: Kruskal-Wallis test

Table (4) Physiological parameters of the PIPP after gentle human touch

Item		Group I	Group II	Group III	Test value	P-value	Sig.
		No. = 30	No. = 30	No. = 30			
Baseline Heart rate	**Mean ± SD**	131.27 ± 11.76	127.43 ± 12.78	133.17 ± 10.22	1.891•	0.157	NS
	Range	108 – 150	103 – 152	110 – 150			
Peak heart rate	**Mean ± SD**	156.10 ± 11.45	161.17 ± 12.89	168.03 ± 8.43	8.766•	0.000	HS
	Range	128 – 178	127 – 187	150 – 182			
Increase in heart rate from baseline	**Mean ± SD**	24.83 ± 9.40	32.97 ± 9.44	34.13 ± 6.57	10.466•	0.000	HS
	Range	9 – 45	14 – 48	18 – 47			
Heart rate 1 min post exam	**Mean ± SD**	144.83 ± 11.10	146.23 ± 11.48	146.47 ± 7.86	0.222•	0.802	NS
	Range	120 – 160	118 – 169	134 – 164			
Baseline saturation	**Mean ± SD**	97.67 ± 1.95	98.00 ± 2.18	98.03 ± 1.75	0.318•	0.729	NS
	Range	94 – 100	94 – 100	95 – 100			
Lowest saturation during exam	**Mean ± SD**	91.73 ± 2.45	91.50 ± 2.33	91.50 ± 1.83	0.110•	0.896	NS
	Range	87 – 95	87 – 95	88 – 95			
Saturation 1min after exam	**Mean ± SD**	96.53 ± 2.85	95.73 ± 2.72	95.43 ± 2.33	1.391•	0.254	NS
	Range	90 – 100	91 – 100	92 – 100			
Difference in saturation	**Mean ± SD**	5.97 ± 1.38	6.50 ± 1.31	6.53 ± 1.07	1.913•	0.154	NS
	Range	4 – 9	5 – 10	4 – 8			
Post hoc analysis							
		Group I Vs group II	**Group I Vs group III**	**Group II Vs group III**			
Peak heart rate		0.080 (NS)	0.000 (HS)	0.019 (S)			
Increase in heart rate from baseline		0.000 (HS)	0.000 (HS)	0.600 (NS)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: One Way ANOVA test

Table (5) Individual behavioral physiological and facial parameters and mean PIPP after gentle human touch

Item		Group I	Group II	Group III	Test value	P-value	Sig.
		No. = 30	No. = 30	No. = 30			
Score GA	Median (IQR)	1 (0 – 1)	1 (1 – 1)	1 (0 – 1)	2.825≠	0.243	NS
	Range	0 – 1	0 – 1	0 – 1			
Behavioural state	Median (IQR)	2 (2 – 2)	2 (1 – 2)	2 (2 – 2)	2.715≠	0.257	NS
	Range	1 – 3	1 – 3	1 – 3			
Brow bulge	Median (IQR)	2 (2 – 3)	2 (2 – 3)	2 (2 – 3)	2.168≠	0.338	NS
	Range	1 – 3	1 – 3	1 – 3			
Eye Squeeze	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	2.516≠	0.284	NS
	Range	2 – 3	2 – 3	2 – 3			
Nasolabial Furrow	Median (IQR)	3 (2 – 3)	3 (2 – 3)	3 (2 – 3)	0.654≠	0.721	NS
	Range	2 – 3	2 – 3	2 – 3			
PIPP HR	Median (IQR)	2 (2 – 3)	2 (2 – 2)	2 (2 – 3)	1.357≠	0.507	NS
	Range	1 – 3	2 – 3	2 – 3			
PIPP Saturation	Median (IQR)	2 (2 – 3)	2 (2 – 2)	2 (2 – 2)	0.030≠	0.985	NS
	Range	1 – 3	2 – 3	2 – 3			
Mean PIPP Score	Median (IQR)	14 (13 – 16)	14 (13 – 16)	15 (14 – 16)	1.473≠	0.479	NS
	Range	11 – 18	12 – 18	12 – 18			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

≠: Kruskal-Wallis test

Table (6) PIPP score before and after gentle human touch in group I

Item		Group I		Test value	P-value	Sig.
		Before human touch	After human touch			
Baseline heart rate	Mean ± SD	131.77 ± 12.73	131.27 ± 11.76	0.828•	0.415	NS
	Range	108 – 160	108 – 150			
Peak heart rate	Mean ± SD	173.60 ± 16.92	156.10 ± 11.45	9.077•	0.000	HS
	Range	128 – 200	128 – 178			
Increase in heart rate from baseline	Mean ± SD	41.43 ± 15.18	24.83 ± 9.40	8.630•	0.000	HS
	Range	17 – 62	9 – 45			
Heart rate 1 min post exam	Mean ± SD	152.97 ± 13.62	144.83 ± 11.10	5.668•	0.000	HS
	Range	120 – 174	120 – 160			
Baseline saturation	Mean ± SD	97.83 ± 2.34	97.67 ± 1.95	1.000•	0.326	NS
	Range	93 – 100	94 – 100			
Lowest saturation during exam	Mean ± SD	91.07 ± 2.86	91.73 ± 2.45	-3.084•	0.004	HS
	Range	85 – 95	87 – 95			
Saturation 1min after exam	Mean ± SD	96.70 ± 3.14	96.53 ± 2.85	4.419•	0.000	HS
	Range	90 – 100	90 – 100			
Difference in saturation	Mean ± SD	6.83 ± 1.32	5.97 ± 1.38	1.095•	0.283	NS
	Range	5 – 10	4 – 9			
GA Score	Median (IQR)	1 (0 – 1)	1 (0 – 1)	0.000≠	1.000	NS
	Range	0 – 1	0 – 1			
Behavioral state	Median (IQR)	3 (2 – 3)	2 (2 – 2)	-4.291≠	0.000	HS
	Range	2 – 3	1 – 3			
Brow bulge	Median (IQR)	3 (2 – 3)	2 (2 – 3)	-3.300≠	0.001	HS
	Range	2 – 3	1 – 3			
Nasolabial furrow	Median (IQR)	3 (2 – 3)	3 (2 – 3)	-1.069≠	0.285	NS
	Range	2 – 3	2 – 3			
Eye squeeze	Median (IQR)	3 (2 – 3)	3 (2 – 3)	-1.414≠	0.157	NS
	Range	2 – 3	2 – 3			
PIPP saturation	Median (IQR)	2 (2 – 2)	2 (2 – 3)	-1.292≠	0.196	NS
	Range	1 – 3	1 – 3			
Mean PIPP Score	Median (IQR)	16 (15 – 17)	14 (13 – 16)	-3.635≠	0.000	HS
	Range	14 – 19	11 – 18			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: Paired t-test; ≠: Wilcoxon Signed Ranks tes

Table (7) PIPP before and after gentle human touch in group II

Item		Group II		Test value	P-value	Sig.
		Before human touch	After human touch			
Baseline heart rate	Mean ± SD	128.90 ± 13.41	127.43 ± 12.78	2.369•	0.025	S
	Range	108 – 152	103 – 152			
Peak heart rate	Mean ± SD	174.17 ± 17.86	161.17 ± 12.89	7.259•	0.000	HS
	Range	127 – 200	127 – 187			
Increase in heart rate from baseline	Mean ± SD	45.10 ± 17.64	32.97 ± 9.44	6.626•	0.000	HS
	Range	14 – 71	14 – 48			
Heart rate 1 min post exam	Mean ± SD	156.47 ± 15.33	146.23 ± 11.48	5.480•	0.000	HS
	Range	118 – 182	118 – 169			
Baseline saturation	Mean ± SD	97.33 ± 2.48	98.00 ± 2.18	-2.660•	0.013	S
	Range	92 – 100	94 – 100			
Lowest saturation during exam	Mean ± SD	90.17 ± 2.77	91.50 ± 2.33	-5.637•	0.000	HS
	Range	85 – 95	87 – 95			
Saturation 1min after exam	Mean ± SD	95.23 ± 3.04	95.73 ± 2.72	2.392•	0.023	S
	Range	88 – 100	91 – 100			
Difference in saturation	Mean ± SD	7.13 ± 1.38	6.50 ± 1.31	-2.628•	0.014	S
	Range	5 – 9	5 – 10			
Score GA	Median (IQR)	1 (1 – 1)	1 (1 – 1)	0.000≠	1.000	NS
	Range	0 – 1	0 – 1			
Behavioral state	Median (IQR)	3 (2 – 3)	2 (1 – 2)	-3.933≠	0.000	HS
	Range	2 – 3	1 – 3			
Brow bulge	Median (IQR)	3 (2 – 3)	2 (2 – 3)	-1.961≠	0.050	NS
	Range	2 – 3	1 – 3			
Nasolabial furrow	Median (IQR)	3 (2 – 3)	3 (2 – 3)	-0.243≠	0.808	NS
	Range	2 – 3	2 – 3			
Eye squeeze	Median (IQR)	3 (2 – 3)	3 (2 – 3)	-0.728≠	0.467	NS
	Range	2 – 3	2 – 3			
PIPP HR	Median (IQR)	3 (2 – 3)	2 (2 – 2)	-3.900≠	0.000	HS
	Range	2 – 3	2 – 3			
PIPP saturation	Median (IQR)	2 (2 – 2)	2 (2 – 2)	-1.069≠	0.285	NS
	Range	1 – 3	2 – 3			
Mean PIPP Score	Median (IQR)	16 (15 – 17)	14 (13 – 16)	-4.132≠	0.000	HS
	Range	14 – 19	12 – 18			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Paired t-test; ≠: Wilcoxon Signed Ranks test

Table (8): PIPP before and after GHT in group III

Item		Group III		Test value	P-value	Sig.
		Before human touch	After human touch			
Baseline heart rate	Mean ± SD	136.40 ± 14.24	133.17 ± 10.22	-2.355•	0.025	S
	Range	108 – 160	110 – 150			
Peak heart rate	Mean ± SD	181.67 ± 10.55	168.03 ± 8.43	-8.866•	0.000	HS
	Range	160 – 200	150 – 182			
Increase in heart rate from baseline	Mean ± SD	45.27 ± 11.52	34.13 ± 6.57	-7.201•	0.000	HS
	Range	25 – 72	18 – 47			
Heart rate 1 min post exam	Mean ± SD	161.07 ± 9.96	146.47 ± 7.86	-7.513•	0.000	HS
	Range	142 – 177	134 – 164			
Baseline saturation	Mean ± SD	97.03 ± 2.19	98.03 ± 1.75	-3.257•	0.003	HS
	Range	93 – 100	95 – 100			
Lowest saturation during exam	Mean ± SD	90.27 ± 2.56	91.50 ± 1.83	-3.725•	0.001	HS
	Range	86 – 94	88 – 95			
Saturation 1min after exam	Mean ± SD	93.37 ± 3.31	95.43 ± 2.33	-1.070•	0.293	NS
	Range	88 – 99	92 – 100			
Difference in saturation	Mean ± SD	6.77 ± 1.07	6.53 ± 1.07	-5.269•	0.000	HS
	Range	5 – 10	4 – 8			
Score GA	Median (IQR)	1 (0 – 1)	1 (0 – 1)	-0.000≠	1.000	NS
	Range	0 – 1	0 – 1			
Behavioral state	Median (IQR)	3 (2 – 3)	2 (2 – 2)	-4.123≠	0.000	HS
	Range	2 – 3	1 – 3			
Brow bulge	Median (IQR)	3 (2 – 3)	2 (2 – 3)	-1.606≠	0.108	NS
	Range	2 – 3	1 – 3			
Nasolabial furrow	Median (IQR)	3 (2 – 3)	3 (2 – 3)	-0.577≠	0.564	NS
	Range	2 – 3	2 – 3			
Eye squeeze	Median (IQR)	3 (2 – 3)	3 (2 – 3)	-0.500≠	0.617	NS
	Range	2 – 3	2 – 3			
PIPP HR	Median (IQR)	3 (2 – 3)	2 (2 – 3)	-3.207≠	0.001	HS
	Range	2 – 3	2 – 3			
PIPP saturation	Median (IQR)	2 (2 – 2)	2 (2 – 2)	-1.000≠	0.317	NS
	Range	1 – 3	2 – 3			
Mean PIPP Score	Median (IQR)	16 (15 – 17)	15 (14 – 16)	-3.807≠	0.000	HS
	Range	13 – 19	12 – 18			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

•: Paired t-test; ≠: Wilcoxon Signed Ranks test