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ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Physical Medicine and Rehabilitation /Fiziksel Tıp ve Rehabilitasyon

Timing of Cryotherapy Affects the Intensity of Pain Associated with Ultrasound-Guided Musculoskeletal Injection: A Retrospective Study

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ABSTRACT

Objectives: Cryotherapy is a well-known technique used to provide analgesia, especially in the early treatment of musculoskeletal injuries. This study aims to evaluate the effectiveness of pre-injection, post-injection, and combined cryotherapy on pain intensity associated with ultrasound-guided musculoskeletal injection.

Methods: In this retrospective study, a total of 120 participants who had received an ultrasound-guided musculoskeletal injection were subsequently categorized into four groups according to the timing of cryotherapy: PRE (cryotherapy only before injection), POST (cryotherapy only after injection), BOTH (cryotherapy both before and after injection), CON (no cryotherapy). Participants' visual analogue scale (VAS) scores before, during and after the injection were compared.

Results: Timing of cryotherapy had a significant effect on VAS Score ($p < 0.001$). Lowest VAS scores after injection were observed when cryotherapy was applied both before and after injection (0.63 ± 0.12).

Conclusion: Cryotherapy before and/or after injection decreases VAS scores either during injection and/or after injection. Also, the downward trend in VAS scores across all time intervals appears only when cryotherapy was applied both before and after injection.

Keywords: Cryotherapy, Musculoskeletal disorders, VAS Score

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Kriyoterapinin Zamanlaması Ultrason Eşliğinde Kas-İskelet Enjeksiyonu ile İlişkili Ağrının Yoğunluğunu Etkiler: Retrospektif Bir Araştırma

ÖZET

Amaç : Kriyoterapi, özellikle kas-iskelet sistemi yaralanmalarının erken tedavisinde analjezi sağlamak için kullanılan, iyi bilinen bir tekniktir. Bu çalışma, enjeksiyon öncesi, enjeksiyon sonrası ve kombine kriyoterapinin ultrason eşliğinde kas-iskelet sistemi enjeksiyonu ile ilişkili ağrı yoğunluğu üzerindeki etkinliğini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Ultrason eşliğinde kas-iskelet enjeksiyonu yapılmış olan toplam 120 katılımcı, kriyoterapi uygulamasının zamanlamasına göre sonradan dört gruba ayrıldı: PRE (sadece enjeksiyondan önce kriyoterapi), POST (sadece enjeksiyondan sonra kriyoterapi), BOTH (hem enjeksiyondan önce hem de sonra kriyoterapi), CON (kriyoterapi yok). Katılımcıların enjeksiyon öncesi, sırası ve sonrasında görsel analog skala (VAS) skorları karşılaştırıldı.

Bulgular: Kriyoterapi uygulamasının zamanlamasının VAS Skoru üzerinde anlamlı bir etkisi vardı ($p<0,001$). Enjeksiyon sonrası en düşük VAS skorları, enjeksiyon öncesi ve sonrası kriyoterapi uygulandığında gözlendi (0.63 ± 0.12).

Sonuç: Enjeksiyondan önce ve/veya sonra kriyoterapi uygulaması, enjeksiyon sırasında ve/veya enjeksiyondan sonraki VAS skorlarını düşürür. Ayrıca, tüm zaman aralıklarında VAS puanlarındaki düşüş eğilimi, yalnızca enjeksiyondan önce ve sonra kriyoterapi uygulandığında ortaya çıkar.

Anahtar Sözcükler : Kriyoterapi, Kas-iskelet sistemi problemleri, VAS skoru

An ultrasound-guided injection is one of the effective treatment options in musculoskeletal diseases (1-3). Ultrasonography has become widely used during injection due to visualization of needle placement, distribution of the injected material, and surrounding anatomical structures in real-time, thus minimizing the risk of injury and maximizing the benefit from treatment (4,5). Along with other complications, the pain associated with the procedure can be reduced by minimizing the trauma in the local tissue and the number of attempts required to perform the procedure, however pain may still be present in patients who undergo these procedures (6,7).

Cryotherapy is a well-known technique used to provide analgesia, especially in the early treatment of musculoskeletal injuries (8). Cryotherapy increases the excitability threshold of sensory neurons at the site of application as a result of the decrease in neuronal metabolism and sodium-potassium pump activity, thereby providing the analgesic effect by decreasing the nerve conduction velocity (9). Additionally, cryotherapy provides the analgesic effect by decreasing cell metabolism, vasoconstriction, and reduction of metabolic waste, inflammation and muscle spasm (10). Although there are many methods for cryotherapy, such as ice towels, ice massage, gel packs, refrigerant gases, and inflatable splints, ice pack application is more preferred in daily practice because it is inexpensive and easily available (11).

The effects of cryotherapy or ice application on pain reduction have generally been studied for intra-oral injections (12), local anesthetic injection (13), and Botulinum toxin injections (14). Despite the well-known analgesic effect of cryotherapy and its place in the musculoskeletal standard of care, to the best of our current knowledge, there is no study in the literature evaluating the effect of cryotherapy on the intensity of pain associated with the ultrasound-guided musculoskeletal injection. Therefore, this study aimed to investigate the effectiveness of pre-injection, post-injection, and combined cryotherapy application on pain intensity associated with ultrasound-guided musculoskeletal injection, specifically during and after injection.

METHODS

This study received approval from Local Medical Ethics Committee and followed the guidelines of Declaration of Helsinki.

Participant Selection

Patients who had received a therapeutic injection treatment for a musculoskeletal disease or injury between March 2020 and March 2021 were selected. Patients who received local anesthetic injections, patients with comorbid diseases which may interfere with their sensation of pain were excluded from the study. Accordingly, a total of 120 participants were retrospectively included in the study. Participants were categorized into four groups according to the cryotherapy application before and/or after the injection: PRE (cryotherapy applied before injection), POST (cryotherapy applied after injection), BOTH (cryotherapy applied both before and after injection), CON (control group consisting of participants who had no cryotherapy at all). There were 30 participants in each group.

Participants' demographics (age, sex, level of education, smoking status), anthropometrics (body weight, height, body mass index), diagnosis, existence of comorbid diseases, type of the injected medication (hyaluronic acid, platelet-rich plasma (PRP), corticosteroids), injected anatomical region were noted, as well as VAS scores reported before, during and after the injection.

Cryotherapy and Injections Procedures

All injections were performed ultrasound-guided by the same sports medicine specialist (AE). Cryotherapy was applied by a cooling pad (28 X 29 -cm) wrapped in a waterproof cover. The cooling temperature was of 5 ^{o}C. Each ice pack application was done for 5 minutes. When cryotherapy was applied both before and after the injection, total time of application was 10 minutes.

Participants had received either hyaluronic acid, corticosteroid (1 ml of 40mg/ml methylprednisolone acetate) or a PRP injection. PRP had been prepared as described (15): Fifty milliliters (50 mL) of blood was collected from patients' veins in antecubital fossa into sodium citrate containing tubes. Tubes were centrifugated twice, first at 1500 rpm for 6 minutes, and second at 3500 rpm for 12 minutes. After the first spin, upper layer of plasma was transferred to empty sterile tubes. After the second spin, platelet pellets with few red blood cells at the bottom were collected and were homogenized by thoroughly mixing it with the upper 1/3rd of the plasma. Lower 2/3rd was discarded. PRP was activated by adding 1 mL 10% calcium chloride. Later the injection was performed.

Visual Analogue Scale

Patients were asked to rate the intensity of their pain on a 100-mm VAS. The scale was positioned horizontally and ends were labeled with the remarks "the least possible pain" and "the worst possible pain". VAS scores were collected from patients at arrival, during injection, and 10 minutes after the injection right before leaving the outpatient clinic. VAS is a valid and reliable tool for assessing the intensity of both chronic and acute pain (16,17).

Statistical Analysis

The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov test) to determine normal or non-normal distributions. Descriptive analyses are presented using mean ± standard deviation (SD) and standard error of mean (SEM) for continuous variables and using frequency counts and percentages for categorical variables. Participants' characteristics were compared between groups by running either an analysis of variance test for continuous variables or a chi-square test for categorical variables. A two-way mixed analysis of variance test was performed for comparing the changes in VAS scores at three time-points between groups (between factor: group, within factor: time). For post-hoc analysis, a series of pairwise T tests were performed with Bonferroni correction. All analysis was performed using R Studio, Version 3.6.2. Statistical significance was accepted as $p < 0.05$.

RESULTS

Participants' characteristics are given in Table 1. The study groups had similar characteristics with each other. Participants were diagnosed with the following conditions: Supraspinatus tenosynovitis/partial rupture (n=29), chondromalacia patella (n=21), gonarthrosis (n=18), lateral epicondylitis (n=17), meniscopathy (n=11), Achilles tendinopathy (n=10), coxarthrosis (n=5), anterior talofibular ligament sprain (n=4), DeQuervain tenosynovitis (n=2), calcaneal spur (n=2), and Morton's neuroma (n=1).

Mean VAS scores with SEM are given in Table 2. Figure 1 shows the changes in VAS scores across time points. The cumulative probability plot presented in Figure 2 demonstrates the divergence of VAS improvement on the participant level with the most improvement in the BOTH group. A two-way mixed analysis of variance test was run in order to evaluate the effect of time, group, and time:group interaction on VAS scores. All three had significant effect on VAS score (effect of time: $F(2,232) = 245.332$, $p < 0.001$; effect of group: $F(3,116) = 14.764$, $p < 0.001$; effect of time:group interaction: $F(6,232) = 58.164$, $p < 0.001$).

The simple main effect of group was found significant at all three time points (Before injection: $F(3,116) = 8.40$, $p < 0.001$; During Injection: $F(3,116) = 29.6$, $p < 0.001$; After Injection: $F(3,116) = 58.0$, $p < 0.001$).

Pairwise comparisons showed similar baseline VAS scores among these groups: PRE vs. POST, PRE vs. CON, CON vs. POST, and BOTH vs. POST ($p > 0.99$, $p = 0.3$, $p = 0.08$, and $p = 0.08$, respectively.) However, baseline VAS measurements varied significantly among the groups BOTH vs. PRE and BOTH vs. CON ($p = 0.002$ and $p < 0.001$, respectively). During injection, the difference between VAS scores were insignificant among groups who received ice application prior to injection (PRE vs. BOTH, $p > 0.99$) and who did not receive any ice application prior to injection (POST vs. CON, $p > 0.99$). On the other hand, comparisons between the groups who received cryotherapy before injection and the groups that did not, showed significant results: PRE vs. POST, PRE vs. CON, POST vs. BOTH, POST vs. CON (all $p < 0.001$). All pairwise comparisons of VAS scores between groups after the injection were significant at $p < 0.01$.

The simple main effect of time was also found significant for all groups (CON: $F(2,58) = 4.96$, $p = 0.04$; PRE: $F(2,58) = 71.8$, $p < 0.01$; POST: $F(2,58) = 64.9$, $p < 0.01$; BOTH: $F(2,58) = 306.0$, $p < 0.01$).

Although the simple main effect of time was significant for the CON group as well, the pairwise comparisons showed that, in the CON group, VAS scores did not change significantly between timepoints (Before vs. During: $p = 0.2$, Before vs. After: $p > 0.99$, During vs. After: $p = 0.2$). In the PRE group, comparisons of VAS scores between Before vs. During, and Before vs. After were both significant at $p < 0.001$, whereas the difference between During vs. After was insignificant ($p > 0.99$). In the POST group, results of the comparisons between Before vs. During was insignificant ($p > 0.99$), whereas there was significant change between Before vs. After and During vs. After ($p < 0.001$, both). Finally, in the group BOTH, all pairwise comparisons were significant ($p < 0.001$, all).

Table 1: Participants characteristics						
		PRE (n=30)	**POST (n=30)**	**BOTH (n=30)**	**CONTROL (n=30)**	**p**
Age, years		50.63±8.63	50.53±10.97	52.5±9.04	47.63±9.48	F(3,116)= 1.27716 p= 0.285
Sex	Male	14 (46.7%)	10 (33.3%)	9 (30%)	11 (36.7%)	$X^2(3,120)=2.009$, p=0.57
	Female	16 (53.3%)	20 (66.7%)	21 (70%)	19 (63.3%)	
Body Weight, kg		74.76±9.68	76.6±9.90	76.2±13.97	78.63±11.35	F(3,116)= 0.57276, p= 0.634
Height, cm		173.16±7.95	172.4±7.79	172.1±8.75	173.8±6.68	F(3,116)= 0.27833, p= 0.840
Body Mass Index, kg/m²		24.97±3.26	25.85±3.64	25.6±3.92	26.03±3.46	F(3,116)= 0.57025, p= 0.635
Level of Education	University	27 (90%)	25 (83.3%)	27 (90%)	27 (90%)	$X^2(3,120)=0.9704$, p=0.808
	High School	3 (10%)	5 (16.7%)	3 (10%)	3 (10%)	
Smoking	Smoker	1 (3.3%)	1 (3.3%)	3 (10%)	1 (3.3%)	$X^2(6,120)=5.4608$, p=0.486
	Nonsmoker	12 (40%)	9 (30%)	9 (30%)	6 (20%)	
	Quit Smoking	17 (56.7%)	20 (66.7%)	18 (60%)	23 (76.7%)	
Comorbid Diseases†	Yes	6 (20%)	7 (23.3%)	7 (23.3%)	6 (20%)	$X^2(3,120)=0.1964$, p=0.978
	No	24 (80%)	23 (76.7%)	23 (76.7%)	24 (80%)	
Anatomical region of injection‡	Hand&Wrist	0 (0%)	1 (3.3%)	0 (0%)	1 (3.3%)	$X^2(9,120)=7.1432$, p=0.622
	Elbow	6 (20%)	3 (10%)	6 (20%)	2 (6.6%)	
	Shoulder	10 (33.3%)	6 (20%)	4 (13.3%)	9 (30%)	
	Hip	1 (3.3%)	0 (0%)	0 (0%)	4 (13.3%)	
	Knee	10 (33.3%)	14 (46.7%)	16 (53.3%)	10 (33.3%)	
	Foot&Ankle	3 (10%)	6 (20%)	4 (13.3%)	4 (13.3%)	
Site of Injection §	Right	23 (92%)	20 (76.9%)	18 (78.3%)	24 (85.7%)	$X^2(3,102)=2.6616$, p=0.446
	Left	2 (8%)	6 (23.1%)	5 (21.7%)	4 (14.3%)	
Dominance of the injected site §	Dominant	18 (81.8%)	15 (65.2%)	15 (75%)	17 (80.9%)	$X^2(3,86)=2.1342$, p=0.545
	Non-dominant	4 (18.1%)	8 (34.8%)	5 (25%)	4 (19.1%)	
Intraarticular injection	Yes	11 (36.7%)	15 (50%)	18 (60%)	18 (60%)	$X^2(3,120)=4.4049$, p=0.220
	No	19 (63.3%)	15 (50%)	12 (40%)	12 (40%)	
Injected medication	Sodium Hyaluronate	6 (20%)	9 (30%)	12 (40%)	7 (23.3%)	$X^2(9,120)=3.7087$, p=0.716
	PRP	16 (53.3%)	14 (46.7%)	12 (40%)	14 (46.6%)	
	Corticosteroid	8 (26.7)	7 (23.3%)	6 (20%)	9 (30%)	

Data is displayed as either "mean ± standard deviation" or "n (%)". †Comorbid diseases: PRE: Hypertension (n=5), Asthma (n=1); POST: Hypertension (n=4), Asthma (n=2), Coronary Artery Disease (n=1); BOTH: Hypertension (n=5), Asthma (n=1), Hypercholesterolemia (n=1); CONTROL: Hypertension (n=4), Asthma (n=1), Peripheral vascular disease (n=1). ‡Grouped as 4 categories (hand&wrist&elbow, shoulder, hip&knee, foot&ankle) for a more accurate analysis. §Site of injection and dominance were not available in all patient charts, hence missing data.

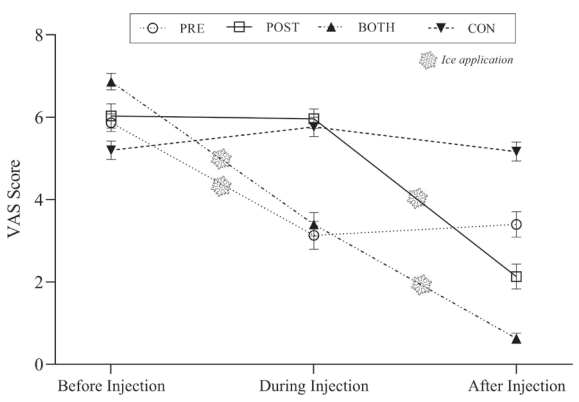

Figure 1: *VAS Scores of participants.*
Error bars show standard error of mean. Ice symbol denotes the timing of cryotherapy.

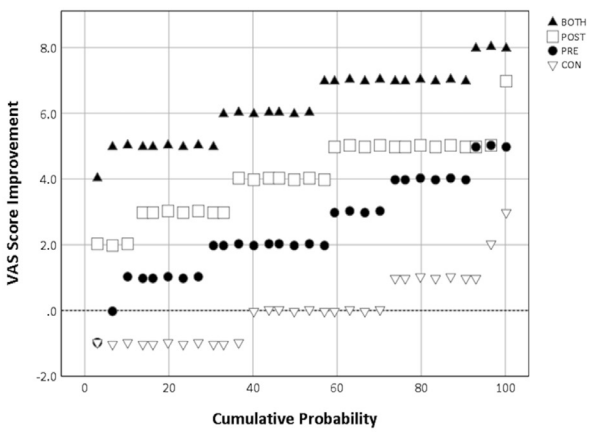

Figure 2: *Cumulative probability plot of VAS score improvements (pre-injection VAS –*
post-injection VAS) in the participants.

Table 2: Visual analogue scale (VAS) scores of participants at different time points.

Group	Time of Measurement	Mean VAS Score	Standard Error of Mean
PRE	Before Injection &	5.87	0.21
	During Injection #ϕ	3.13	0.33
	After Injection #&ϕ	3.40	0.30
POST	Before Injection	6.03	0.29
	During Injection *&	5.97	0.23
	After Injection *&ϕ	2.13	0.30
BOTH	Before Injection *ϕ	6.87	0.20
	During Injection #	3.40	0.28
	After Injection *#ϕ	0.63	0.12
CON	Before Injection &	5.2	0.22
	During Injection *#	5.7	0.23
	After Injection *#&	5.1	0.23

**Significantly different than PRE at the same timepoint (P<0.001), #Significantly different than POST at the same timepoint (P<0.001), &Significantly different than BOTH at the same timepoint (P<0.001), ϕSignificanlty different than CON at the same timepoint (P<0.001).*

DISCUSSION

The objective of this study was to investigate the effect of cryotherapy on pain intensity associated with ultrasound-guided musculoskeletal injection procedures. To the best of our current knowledge, this is the first study to demonstrate the effectiveness of cryotherapy on pain associated with musculoskeletal injection therapy. In this sense, the important aspect of our study would be the fact that it proves the knowledge that cryotherapy, which is widely used in daily clinical practice to reduce pain intensity without sufficient data in the literature, reduces pain during and after injection.

We noted statistically significant decreases in the intensity of pain felt during injection compared to pre-injection in the PRE and BOTH groups, but such a reduction was not present in either the POST or the CON groups. Accordingly, in cases where low pain intensity is desired during the musculoskeletal injection procedure, cryotherapy before injection might be recommended. Similarly, patients may experience pain during botulinum toxin type-A injection, which may cause discomfort for both the patient and the physician who apply the treatment. In a prospective, randomized, single-blind controlled study, the authors evaluated the effect of cryotherapy on the treatment zone before botulinum toxin type-A treatment on the pain felt during injections (16). Similar to our results, the authors found that pain is significantly reduced on the side where cryotherapy is applied.

We also observed statistically significant reductions in the pain intensity after injection compared to during injection in the POST and BOTH groups, while such a decline was not present in either the PRE or the CON groups. Additionally, we observed a significant decrease in post-injection VAS scores in the PRE, POST, and BOTH groups compared to pre-injection. However, there was no significant change in post-injection VAS scores in the CON group compared to pre-injection. Furthermore, a downward trend in VAS scores was observed only in the BOTH group across all time intervals. For this reason, both pre-injection and post-injection cryotherapy application might be recommended to reduce injection-related pain, both during and after injection.

Şahin et al. aimed to investigate the effect of the Buzzy application, which is a device that combines cold, vibration, and distraction, on pain and satisfaction during gluteal intramuscular injections of diclofenac sodium (18). The authors compared only the post-injection VAS scores of the application and control groups, and they found that the post-injection VAS scores were statistically significantly lower in the application group. The strengths of our study are grouping participants into four, as three of the study groups having cryotherapy application at different times and the control group having no cryotherapy application, and evaluating the differences in VAS scores between groups as well as the change in VAS scores within the group.

Apart from the abovementioned studies, the effects of cryotherapy or ice application on pain reduction have also been studied in the field of dentistry. In a randomized cross over study, which compared the effectiveness of ice and lidocaine 5% gel for topical anesthesia of oral mucosa, the authors found that using ice for topical anesthesia of oral mucosa before the dental injection caused lower VAS pain scores in comparison to using lidocaine gel (19) . The authors concluded that using ice, as the cheap and readily available method, for topical anesthesia of oral mucosa before the dental injection is effective.

Commonly used methods for cryotherapy are ice packs, ice towels, ice massage, gel packs, refrigerant gases, and inflatable splints. Lathwall et al. compared the efficacy of different precooling agents (ice cone and refrigerant) and topical anesthetics (benzocaine) on pain perception during intraoral injection in pediatric dentistry, and they observed lower mean VAS scores in the ice cone group as compared to refrigerant and benzocaine (12). The authors explained the increased effectiveness of ice compared to the refrigerant, possibly due to increased contact time with tissues. In another study, Bechara et al. investigated whether skin cooling decreases pain during the botulinum toxin type-A injection for patients with focal axillary hyperhidrosis (20). Participants were divided into two groups as follows: Group 1: Skin cooling with cold air system and no cooling on the other side; Group 2: Skin cooling with cold air system and ice cubes on the other side. Contrary to the results of Lathwall et al. (12), the authors found that ice and air cooling reduces pain during injection with the same effectiveness in patients with focal axillary hyperhidrosis (20). In this study, we used only ice packs for cryotherapy application without applying refrigerant or other cryotherapy methods in any study group. For this purpose, further studies might be planned to evaluate the pain reduction effectiveness of different cryotherapy agents during and after musculoskeletal injections.

Matthew et al. conducted a study on patients undergoing Mohs micrographic surgery with local anesthesia, and the authors aimed to determine whether nitrous oxide, ice, vibration, or topical anesthetic improves analgesia for local anesthetic injections (21). The authors found that nitrous oxide, ice, and vibration caused a decrease in the post-injection pain VAS score compared to pre-injection, in the order of the most to the least in the decrease. In addition to that, the authors reported an association of higher pain scores with age <50 years, male sex, and surgery on the nose, lip, ear, or eyelid. In this study, the evaluation of the relationship between pain scores and patient characteristics was not our primary purpose; in fact, we specifically aimed to assess the differences in the injection pain intensity according to the time of ice application. Furthermore, in all four groups, participants had similar characteristics, including age, sex, anthropometric measures, comorbid diseases, the anatomical region, and site of injection, whether the injection is intra-articular or not, and the type of the injected medication.

This study has also some limitations. The first of the limitations in our study was that not all of the joint injection groups were the same joint type. Joints closer to the skin surface, such as the lateral epicondyle or de quervein tenosynovitis, could be compared among themselves, and deeper joints such as the shoulder and knee could be compared within themselves. A secondary limitation was the use of the same ice application time to the superficial and deep joints. Although there is no clear time for applying ice to which joint, how often and for how long in the literature, one of the points to be considered in future studies may be the duration of the application.

CONCLUSION

In conclusion, cryotherapy before and/or after injection decreases VAS scores either during injection or after injection. The advantage of the cryotherapy technique is that it is inexpensive, easily available, and effective in reducing pain, which might be caused by musculoskeletal injection treatment.

DECLARATIONS

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Conflict of Interest: The author declares that there is no conflict of interest

Ethics Approval: This study received approval from Local Medical Ethics Committee (02.04.21/3174).

Availabality of Data and Material: The materials described in the manuscript will be freely available to any scientist wishing to use them for noncommercial purposes, without breaching participant confidentiality.

Author Contributions: MPY, SST writing the original draft, review and editing, MPY,SST,AE conceptualization, formal analysis, investigation, methodology. AE data collection.

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