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ABSTRACTS:
Gender, age and ethnic differences in pain perception have been reported in clinical and experimental research. However, it is not known whether cold and ischemia-induced pain models can explain ethnic-related variability in pain perception. The current study was designed to investigate the effect of ethnicity on pain perception in healthy Nigerians and to assess whether the variability in pain perception is dependent on the circulating level of β-Endorphin. One hundred and sixty healthy volunteers were randomly selected from the four main ethnic groups (Fulani, Hausa, Igbo and Yoruba) in Nigeria. There were 40 volunteers per group. The selected individuals were informed on what they should expect during the study after which their informed consents were requested. Questionnaires were used to obtain the socio-demographic and biodata of each of the consented volunteers. Cold, ischemia and cold+ischemia- induced pains were administered, after which the pain threshold and tolerance were estimated by monitoring the time (seconds) taken for pain to occur and the point at which the subject can no longer withstand the pain. Our results show that Igbo ethnic group has significantly lower threshold in cold-induced pain and significantly higher threshold/tolerance in ischemia-induced pain. No significant difference in pain threshold of all the four ethnic groups during cold+ischemia-induced pain. However, the pain tolerance was significantly higher in Igbo ethnic group when compared with Hausa, Fulani and Yoruba ethnic groups. In addition, the pain tolerance significantly decreased in Hausa and Yoruba compared to Fulani ethnic group, while the pain tolerance was significantly higher in Yoruba ethnic group compared with Hausa ethnic group. Also, the circulating β-Endorphin decreases in all the subjects. The present study demonstrates that ethnicity causes variability in pain perception and this is accompanied with alteration in circulating level of β-Endorphin.

Keywords: β-Endorphin, Pain perception, Threshold, Tolerance, Variability, Volunteers.
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INTRODUCTION:

Pain is the commonest reason why people present themselves in health facilities and responses to pain vary from one person to another. Several factors affect pain perception ranging from psychological to physiological [1]. Ethnicity has been reported to play a role in pain perception as study of Nigerian women in labour showed that Yoruba women have the lowest pain tolerance compared to other ethnic groups [2].

However in situation where acute pain progresses to chronic due to poor pain management, there would be a resultant negative effect on the productivity of the community and in addition an increase in the cost of maintaining the health system [3]. The only way to subdue this burden is to individualize pain treatment and this can be achieved through extensive research on pain perception.

Most knowledge and pharmacology of pain has been obtained from animal studies where communication is a significant limitation to accurate pain evaluation. The assessment of pain in such situation is usually through neurophysiological or behavioural responses in animals [4, 5]. Data obtained from animal studies can only be partially applicable to human because of major differences between species making human experiment on pain perception an imperative study, which can also be an ethical challenge. The main limitation to human experimental pain study is based on chronic studies where comorbidity would affect results [6, 7, 8] but ethically approved studies on healthy consented volunteers would likely remove such limitations. Experimental pain in healthy volunteers is also better than clinical trial because it allows tolerant level for pain stimulus and assessment of corresponding responses which will make study of mechanisms and variations easy to understand [7, 9].

When intensity, duration, frequency and location of pain stimulus in relation to pain response are studied in healthy volunteers, the result can help to individualize pain management which will achieve better results. Modalities like electricity, thermal and mechanical are commonly used to mimic pain in human subjects [10]. However, the present study uses thermal, ischemic and combination of both to investigate the effect of ethnicity on pain perception among healthy Nigerians.

SUBJECTS AND METHODS:

One hundred and sixty (160) healthy volunteers were randomly selected from the four main ethnic groups (Fulani, Hausa, Igbo and Yoruba) in Nigeria. There were 40 volunteers per group. The selected individuals were trained on what they should expect during the study after which their informed consents were requested.

Inclusion criteria for the selection of subjects:

The subjects selected were not diabetic, not hypertensive, had normal sensation (touch, pain, vibration and feeling), not on any medications, not on hospital admission in the last one month, did not have surgery done in the last three month, not suffering from chronic pain syndrome, with no comorbidity and were willing to follow the guidelines, in the protocol, and also voluntarily signing the consent form. The investigation was carried out under approval of the Research and Ethical Review Committee of the University of Ilorin, Ilorin, Nigeria.

Protocol:

The subjects were visited in their home and informed about the study; subsequently volunteers were recruited and administered questionnaires to obtain their biodata and socio-demographic data. Subjects were made to sit comfortably in a reclining chair that provides adequate support for the head, arms and legs. The testing facility was at a comfortable room temperature, and provides a quiet and neutral environment with no distraction. Having informed the subject about the procedures and what to expect during the experiment, the following assessments were performed:

Cold-induced pain:

Cold sensation and pain in humans are mediated by Aδ and C fibres. The subjects were asked to hold a cold gel bag maintained at 00C for as long as possible as described by Fowler et al [11].

Ischaemia-induced pain:

The ischaemic pain testing was based on the method by Plesan et al [12], a blood pressure cuff was placed around the non-dominant arm of the subject. The cuff pressure was inflated to 20mmHg above the subject's systolic pressure. With the pressure maintained, subject performed a hand grip exercise on an elastic ball. The subjects closed their eyes for the entire procedure to minimize distraction and time clues. They were asked to indicate when they first detected the pain and when they could no longer tolerate the pain (to a maximum of 5 minutes). Once pain tolerance was reached, the pressure curve was immediately deflated and end-points were measured in seconds (s) with the process performed 3 times and average of the readings documented [12].

Assessment of pain threshold and tolerance:

The pain threshold is defined as the point between being "about to be painful" and "just became painful" and the time taken for this to occur is recorded in seconds, while the pain tolerance is defined as the point at which the subject can no longer withstand the pain. The time taken for this to occur is recorded in seconds. The processes were performed 3 times and the averages were documented [11, 12].

Biochemical Analysis:

Blood sample was collected into EDTA bottles, centrifuged for 30mins at 3000 rpm. The plasma β-Endorphin was determined using ELIZA kit (Cruz Biotechnology, Canada).

All data were expressed as the Mean ± S. E. M. Statistical analysis was performed using SPSS version 20 software. One-way analysis of variance (ANOVA) was used to compare the mean values of variables among the groups. Duncan Post Hoc test was also used to compare significant difference among groups. A difference between two means was considered to be statistically significant when $p < 0.05$.

RESULTS:

Effect of ethnicity on pain threshold and tolerance during cold-induced pain test: The pain threshold was significantly lower ($p<0.05$) in Igbo ethnic group compared with Hausa, Fulani and Yoruba ethnic groups whereas the pain threshold of these ethnic groups (Hausa, Fulani and Yoruba) did not change significantly ($p<0.05$) when compared with one another. However, there was no significant change in pain tolerance of all the four ethnic groups when compared with one another (Table 1).

Effect of ethnicity on pain threshold and tolerance during ischemia-induced pain test: Igbo ethnic group showed significantly higher ($p<0.05$) pain threshold and tolerance when compared with Hausa, Fulani and Yoruba ethnic groups. However, the pain threshold and tolerance did not change significantly in Hausa, Fulani and Yoruba ethnic group when compared with one another (Table 2).

Effect of ethnicity on pain threshold and tolerance during ischemia+cold-induced pain test

The results showed no significant difference ($p<0.05$) in pain threshold of all the four ethnic groups. However, the pain tolerance was significantly higher ($p<0.05$) in Igbo ethnic group when compared with Hausa, Fulani and Yoruba ethnic groups. In addition, the pain tolerance significantly decreased ($p<0.05$) in Hausa and Yoruba compared to Fulani ethnic group, while the pain tolerance was significantly higher in Yoruba ethnic group compared with Hausa ethnic group (Table 3).

Effect of ethnicity on circulating β-Endorphin during cold, ischemia and ischemia+cold-induced pain: The circulating level of β-Endorphin significantly decreased ($p<0.05$) in all the four ethnic groups during cold, ischemia and ischemia+cold-induced pain respectively when compared with control except for Fulani and Yoruba ethnic groups which did not show significant difference in circulating level of β-Endorphin during ischemia+cold-induced pain test (Table 4).

Table 1: Effect of ethnicity on pain threshold (s) and tolerance (s) during cold-induced pain test

Groups	Fulani	Hausa	Igbo	Yoruba
Threshold	63.31±13.12	53.30±10.08	31.80±0.92^{a,b,c}	37.42±2.01
Tolerance	106.12±12.22	101.01±10.26	86.80±15.55	75.20±12.28

Data are expressed as mean ±S.E.M. n=10. Data were analysed by one-way ANOVA followed by Duncan post hoc test. (a,b,c $p<0.05$ relative to Fulani, Hausa and Yoruba respectively).

Table 2: Effect of ethnicity on pain threshold (s) and tolerance (s) during ischemia-induced pain test

Groups	Fulani	Hausa	Igbo	Yoruba
Threshold	28.40±1.03	30.82±2.00	35.90±1.02^{a,b,c}	23.42±2.20
Tolerance	42.10±5.25	43.81±2.80	76.53±8.50^{a,b,c}	39.90±3.18

Data are expressed as mean±S.E.M. n=10. Data were analysed by one-way ANOVA followed by Duncan post hoc test. (a,b,c $p<0.05$ relative to Fulani, Hausa and Yoruba respectively).

Table 3: Effect of ethnicity on pain threshold(s) and tolerance(s) during cold+ischemia-induced pain test

Groups	Fulani	Hausa	Igbo	Yoruba
Threshold	40.70±5.12	37.40±4.05	39.31±5.00	31.20±3.82
Tolerance	90.10±6.21	56.30±5.18^{a}	160.53±6.30^{a,b,c}	72.60±3.82 ^{a,b}

Data are expressed as mean±S.E.M. n=10. Data were analysed by one-way ANOVA followed by Duncan post hoc test. (a,b,c $p<0.05$ relative to Fulani, Hausa and Yoruba respectively).

Table 4: Effect of ethnicity on circulating level of β-Endorphin (pg/ml)

Groups	Control	CIP	IIP	CIP+IIP
Fulani	48.80±2.22	20.80±4.09*	32.60±2.36*	45.80±5.92
Hausa	54.40±3.21	19.20±5.18*	19.20±3.51*	33.40±2.18*
Igbo	65.60±3.50	15.20±2.44*	24.40±2.06*	38.60±2.77*
Yoruba	82.40±4.82	35.60±1.86*	46.40±6.41*	69.60±4.82

Data are expressed as mean±S.E.M. n=10. Data were analysed by one-way ANOVA followed by Duncan post hoc test. (*$p<0.05$ vs control). CIP; cold-induced pain, IIP; ischemia-induced pain

DISCUSSION:

Considerable evidence has substantially demonstrated ethnic disparities in the prevalence, treatment, progression and outcomes of pain-related conditions [3]. However, there is a dearth in information regarding the mechanism underlying these group differences, although the variability has been associated with variation in quality of sleep [13], vitamin D deficiency [14], socio-cultural factors

that affect coping mechanism [15] and variation in neurological processes among others.

Our current findings show that Igbo ethnic group has the lowest pain threshold during cold-induced pain and the highest pain threshold and tolerance during ischemia-induced pain, while Fulani, Hausa and Yoruba do not show significant difference in pain threshold and tolerance during cold and ischemia-induced pain tests respectively. In addition the study shows no significant difference in pain threshold during cold+ischemia-induced pain across the four ethnic groups. However, the pain tolerance is significantly higher in Igbo ethnic group when compared with Hausa, Fulani and Yoruba ethnic groups during cold+ischemia-induced pain. Also, the pain tolerance significantly decreases in Hausa and Yoruba compared to Fulani ethnic group, while the pain tolerance was significantly higher in Yoruba ethnic group compared with Hausa ethnic group during cold+ischemia-induced pain. Also, the circulating levels of β-Endorphin decreases significantly in all the four ethnic groups when compared with control groups during cold or ischemia-induced pain.

The finding that Igbo ethnic group has the lowest threshold during cold-induced pain seems to be in consonance with earlier study which reported that previous exposure to cold and percentage of body fat affect response to cooling [16]. Igbo ethnic group originated from the Riverine area of Nigeria and they are naturally exposed to cold than other ethnic groups.

In addition, our present study indicates that Igbo ethnic group has the highest pain threshold and tolerance when compared with other ethnic groups during ischemia pain: this suggests variability in pain perception between the Igbo and the other ethnic groups in Nigeria. Also, the significant difference in pain tolerance obtained in the present study during cold+ischemia-induced pain test indicates variability in pain perception among the four ethnic groups in Nigeria. Therefore, the present results show that ischemia-induced pain reflects higher pain threshold and tolerance when compared with cold-induced pain in Igbo ethnic group. This implies that cooling may have significant analgesic properties than ischemic pain: this is in agreement with previous study that cooling of the body reduces pain in patient with fibromyalgia syndrome [17, 18], post episiotomy pain [19], and postpartum perinea pain [20]. Cooling also reduces serum levels of inflammatory markers thereby reducing pain perception [21]. Also, some authors have measured various markers of inflammation in subjects exposed to very low temperatures [21]. Banfi and colleague showed that treating top-level rugby players with whole body cooling (WBC) for 1 week led to reduced rates of pro-inflammatory cytokines (IL-2 and IL-8) and increased levels of anti-inflammatory cytokines (IL-10) [23].

Cooling or cold exposure has been shown to activate components of reticular activating system, such as, locus ceruleus and raphe nuclei, which can result in activation of behaviour and increased capacity of central nervous system (CNS) to recruit motor neurons as well as activating the sympathetic nervous system (SNS) [24]. These increases in blood circulation level of β-endorphin and noradrenalin after a session of cold shower has been attributed to presence of high density of cold receptors in skin which send an overwhelming amount of electrical impulses from peripheral nerve endings to the brain leading to increase production of β-endorphin. This has significant analgesic effect and it does not cause dependence or noticeable side effects [25]. β-endorphin is an endogenous peptide opioid derived from pro-opiomelanocortin, a neurohormone secreted by the anterior pituitary into the systemic circulation.

Endorphins are found in regions of the brain involved in the perception of pain, including the nucleus accumbens and the arcuate nucleus. Although the role of plasma β-endorphin in pain regulation is unclear, plasma β-endorphin levels have been reported to correlate inversely with pain levels in cancer pain [26], chronic daily headache [27] and post- operative pain [25].

These findings indicate that plasma β-endorphin levels are lower in patients with poorly controlled pain, and increase with pain relief. In our present study there was significant difference in plasma β-endorphin of all the four ethnic groups compared to the control groups during cold or ischemia-induced pain test. Our result is in consonance with earlier study that β-endorphin inversely correlates with pain severity [2]. Hence the variability in pain perception in the present study is plasma β-endorphin dependent

CONCLUSION:

The present study demonstrates that ethnicity causes variability in pain perception and this is associated with alteration in circulating level of β-Endorphin.

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