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Effect of prehospital topical application of water and other agents on outcome in burn injured patients: A prospective study

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ABSTRACT

Introduction: Topical agents applied to the burn wound as first aid measures have been noted to impact outcomes. The application of cool running water is effective when administered for at least 20 min within 3 h of burn as recommended by the Australian and New Zealand Burn Association. However, the American Burn Association recommends running water for 5 min, and only in minor burns. In Nigeria, there are no guidelines for duration of water application. Other agents are often applied in the prehospital setting despite education against such practices. This study was carried out to determine the practice of prehospital first aid and its impact on outcome of burn injuries.

Method: This was a prospective observational study of all burn injured patients admitted to our burn unit between February 2013 and March 2020.

Result: A total of 335 burn injury patients were included in this study, with a median age of 22 years. Males constituted 54.3 % of the patients. Flame injuries accounted for 60 % of cases, and median TBSA was 20.5 %. Majority of the patients received first aid (80.2 %), with 78.9 % receiving first aid within 30 min of injury. Water was applied for first aid in 53.2 % of patients. Application of water for a period of 5 min was associated with reduced rate of infection($P = 0.023$), hospital length of stay ($P = 0.012$, and mortality($P = 0.001$) compared with water application for 10 min, 20 min or just to extinguish flame. The use of running tap and water from a clean container were associated with reduced rate of infection ($P = 0.041$) and reduced mortality rate ($P = 0.006$) compared with other sources of water. Other agents applied were raw pap (a local custard) over the wound, honey, and raw egg, amongst others. These other agents were used either singly or in combination for a combined total of 205 times in 126 patients. These other topical agents had no statistically significant impact on outcome compared with those who did not receive these agents as first aid.

Conclusion: The application of water for approximately 5 min and the use of running tap water or water from a clean container were associated with improved burn injury outcomes. The use of non-water agents had no statistically significant impact on the outcome measures.

1. Introduction

Burns are a public health challenge worldwide [1]. Globally, they account for approximately 180,000 deaths, and are a major cause of lifelong morbidity [1]. Burns are the fifth leading cause of trauma presentation in the emergency department in Nigeria [2,3]. Most of these injuries are caused by flame, followed by scald [4,5]. The mortality rate in a Nigeria study was 19 %, with factors such as inhalation injury, burn size, and burn depth identified as predictors of mortality [5,6]

Burn injuries are largely preventable [1]. However, when they do occur, early and appropriate first aid measures are important. The measures include stopping the burning process, removal of all clothing associated with the patient prior to the burn injury, using cool running water over the burn area, application of a clean wrap over the patient, pain control, and airway management [7–10]. These measures are aimed at reducing the burn extent and depth, providing comfort, and ultimately improving the burn injury outcome [10–12].

There are conflicting guidelines on the use of cool running water for

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burn first aid. The American Burn Association recommends the topical application of water only in minor burns and for 5 min [13]. WHO recommends running water for at least 30 min [7]. In Australia, it is recommended that cool running water, with a temperature between 12ºC and 20ºC should be applied for at least 20 min within 3 h of burn injury [9,14,15]. The recommendation in the Australian and New Zealand Burn Association is regardless of the burn severity [15]. The use of cool running water has been reported to improve healing and reduce burn depth. This entails availability of water in sufficient supply at the scene of the burn injury. Holbert et al. [16] identified the barriers to adequate burn first aid. These include patients' evaluation of pain as a major priority rather than cooling, emotional and mental health distress of the patient as well as that of patient's relatives, compliance factors, and the environmental. Environmental factors are crucial, as the study identified access to clean, cool, running water as a challenge. Therefore, provision of clean, cool, running water in sufficient quantity as to sustain cooling for about 20 min is essential for improved burn first aid [16]. Despite the burden of burn injuries in Nigeria and the late presentation by these patients, there are no guidelines for the use of topical application of water in burn first aid. The absence of a national guideline might be due to the paucity of research on the effect of burn first aid on the outcome of burn injuries in Nigeria. There is a need therefore, to establish the benefit, if any of the topical application of water in Nigeria. There is also need to evaluate the role of water source on burn outcome.

These burn first aid measures can be provided by paramedics, patient's relatives, healthcare workers, neighbors and bystanders at the time of accident [9,17]. Unfortunately, Pasha et al. [18] from Pakistan demonstrated that knowledge of burn first aid is poor, especially in developing countries where burn is more common. Olaitan et al. [19] in a Nigerian study demonstrated that only 10.2 % of burn injury patients had water applied in any combination for first aid, with the majority of the patients using various combinations of raw eggs as the major form of first aid for wound care. WHO and the ABA guidelines frown at the application of any other agents on burn wounds [1,13]. These agents are thought to increase the risk of burn wound infection as well as worsen the outcome of burn injuries. Therefore, these agents are not recommended for burn first aid, as application to the wound is said to promote burn wound infection [1,20]. In Nigeria, however, these agents are regularly applied on the burn wounds prior to presentation at the burn centre.

There is paucity of literature on the impact of topical application of water and other agents on the outcome of burn injury in our sub-region. There is also paucity of literature on the role of water source and duration of application on the outcome of these injuries. The aim of this study was to identify the components of burn injury first aid practiced among burn victims in western Nigeria, and to determine the impact of these practices on burn injury outcome. The outcome measures for this study were the length of hospital stay, the mortality rate, and wound infection. This study will provide information that will be valuable in burn awareness and enlightenment campaigns. The effects of these agents on outcome measures will provide a local experience for burn care educators which will enhance the content and delivery of such awareness campaign. Additionally, the result of this study will provide a framework for more local studies and the development of a national guideline by the Nigerian Burn Injury Society.

2. Method

2.1. Study setting

Our burn center is a 12-bed burn facility located in the premier teaching hospital in Nigeria. This teaching hospital is 1229-bed hospital located in Ibadan, the third largest city in Nigeria [21,22]. It serves as a referral facility for Oyo state and a number of adjoining states located in the south western region of Nigeria.

2.2. Study design

This was a prospective observational study carried out in a major burn center in western Nigeria between February 2013 and March 2020. The study was carried out in accordance with the Helsinki declaration both in the data collation and analysis. The study did not cause any harm to the participant since it only evaluated the impact of the prehospital activties of the patients. All agents applied and the duration of application were done prior to the patients' presentation at the burn centre.

2.3. Inclusion and exclusion criteria

All burn injury patient admitted for inpatient care were included. The admission criteria included burn injury greater than or equal to 15 % total body surface area (TBSA), burn injuries in extremes of age, burn in special areas, as well as burn injuries requiring burn wound excision and grafting. Patients whose burn injury could be managed on outpatient were excluded. Patients with non-special area burn with superficial partial thickness injuries less than 15 % are managed on outpatient as their wounds usually heal within two weeks. They were excluded since the assessment of the outcome measures (rate of burn infection, length of hospital stay, and mortality) would be difficult in this category of patients.

2.4. Data collection and analysis

Patient's age, gender, date of injury, time of injury, cause of injury, and place of occurrence of injury were collected with a proforma. Other variables included administration of first aid, components of the first aid given, the interval between injury and first aid, the person who administered the first aid, and the level of awareness of the first aid administrator. Also contained in the proforma are the duration of water application for the first aid, the source of water, clinical evidence of wound infection, length of hospital stay, and the clinical outcome of burn management. The duration of water application at the prehospital setting was categorized into approximately 5 min, 10 min, 15 min, 20 min, more than 20 min, and water used just for extinguishing the flame on the patient.

The time interval between injury and first aid was categorized into less than or equal to 30 min, 30 min to 1 h, and greater than 1 h. Wound infection was defined by the presence of two or more of the following parameters: temperature (<36ºC or >39ºC), tachycardia (>110 beats per minute), tachypnoea (>25 breaths per minute), thrombocytopenia (<100,000/ul at least 3 days after resuscitation), hyperglycemia, feed intolerance > 24 h, and burn wound discharge[23]. Tissue biopsy for microscopy, culture, and sensitivity was also done following clinical diagnosis of burn wound infection. Tissue biopsy was used for a semi quantitative culture evidence (the organism(s) identified, and the yield described as either scanty, moderate, or heavy growth). The microbiological evidence used for this study was the presence of micro-organism in the tissue biopsy specimen. The criteria were applied universally. Histological evidence of infection was not part of the diagnostic process.

The clinical outcomes of burn management were discharge or mortality. For the purpose of regression analysis, duration of water application was further regrouped into 5 min and more than 5 min. Similarly, water source was also regrouped into two. Running tap and water from clean container were grouped as clean water, while water from any container or unsure source ware grouped as unsure.

Data were coded and entered into SPSS version 27, and analyzed. Inferential statistics was done using Chi-square test and regression analysis at a confidence interval of 95 %, and p-value of 0.05. A p-value of less than 0.05 was statistically significant. The length of hospital was categorized into less than or equal to the median length of stay and greater than the median length of stay. Results are presented in text, tables, and charts.

3. Results

3.1. Basic demographic and burn injury characteristics of the patients

A total of 335 burn injury patients were included for this study, with a median age of 22 years. Males constituted 54.3 % of the patients, while females accounted for 42.4 % The gender was not specified in 3.3 % of the patients. The injuries were majorly flame (60 %) and scald (33.1 %). Chemical injuries (2.4 %), electrical (3.6), and drugs (0.9 %) were the other causes of burn injuries. The median TBSA was 20.5 %. Majority of the injuries occurred at home (62.7 %). The workplace (11.6 %), outdoor (14.3 %), conveyance (9.3 %), unreported (2.1 %) were the other places of burn injury occurrence. Regarding the time of injury, 32.5 % occurred in the morning, 30,1 % in the evening and 26 % in the afternoon. The time was not specified in 11.3 %.

3.2. Basic first aid characteristics

Most of the patients (80.2 %, n = 269) had first aid given following injury, with only 19.8 % (n = 66) receiving no form of first aid. Family members were involved in the administration of first aid in majority of the cases (47.9 %), Fig. 1. Only about 9 % of first aid providers had no enlightenment about burn first aid, Fig. 2. Among those who received first aid, 78.9 % received first aid within 30 min of injury, 9.1 % within 30 min to 1 h, 8.7 % after 1 h, while 3.3 % were unsure of the time interval.

3.3. First aid measures received by the patients

A little over half (53.2 %, n = 143) of the patients had cool water over the burn wound as first aid, with 46.8 % (n = 126) receiving other forms of first aid over their wounds. Other forms of first aid received were raw pap (a local custard) over the wound, honey, raw egg amongst others, Fig. 3. These other agents were used either singly or in combination for a combined total of 205 times in 126 patients. Among those that had water applied over their wounds, majority (58.3 %) had it for only 5 min, with 10 min (13.7 %), 20 min (5.8 %), more than 20 min (0.7 %), just for extinguishing flame (21.6 %) accounting for the remainder of cases. Those who had water applied only for extinguishing flame were older, and had larger TBSA (Table 1). The sources of water were running tap (25.2 %), clean water from container (38.1 %), any water around (20.9 %), and unsure source (15.8 %).

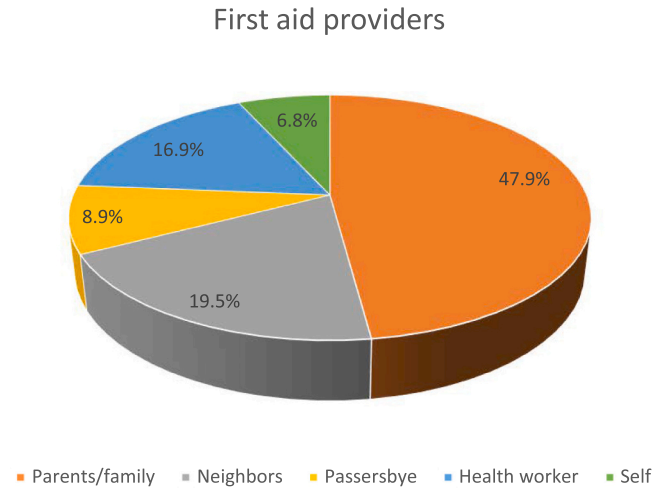

Fig. 1. First aid providers. Family members constitute the majority of first aid administrators.

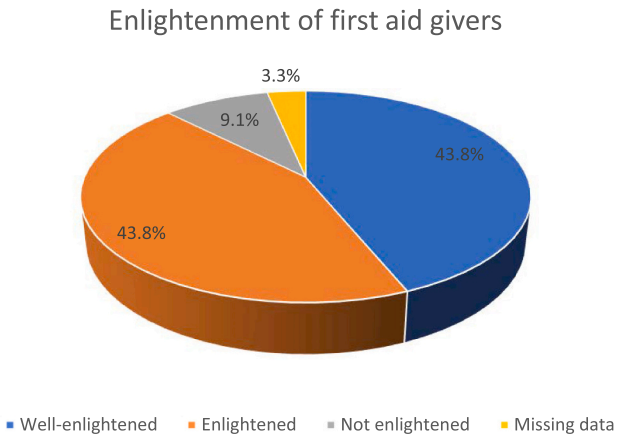

Fig. 2. Enlightenment of first aid givers showing that most of first aid givers were enlightened.

3.4. Duration of water application and burn injury outcomes

There was a statistically significant association between duration of water application and the rate of wound infection, with lower infection rate in those that applied water for only 5 min (X = 11.390, p = 0.023), Table 2. The length of hospital stay was also significantly associated with duration of water application, with majority of those that applied water for more than 5 min having longer hospital stay (X = 12.868, P = 0.012), Table 2. Mortality was lowest among those that had water applied for only 5 min compared to the other groups (X = 33.801, p = 0.001), Table 2. The positive effect of water applied for 5 min on rates of burn infection and mortality were sustained in a regression analysis, however the effect on length of hospital stay was not statistically significant, Table 3.

3.5. Source of water and burn injury outcomes

The source of water applied also had significant impact on the outcome of burn injuries. Those that used running tap water had lower rate of wound infection (X = 8.260, p = 0041), Table 2. Mortality rate was lowest in those that used running tap water, and highest in those unsure of water source (X = 23.213, p = 0.006), Table 2. There was however no significant impact on length of hospital stay by water source (X = 2.538, p = 0.468), Table 2. These effects were sustained in a regression analysis, Table 3.

3.6. Other agents applied and burn injury outcomes

The use of other identified agents did not significantly affect the rate of wound infection (X = 0.008, P = 0.930), Fig. 4; the length of hospital stay (X = 0.167, p = 0.683), 5; and the mortality rate (X = 5.730, p = 0.126), Figs. 5 and 6.

4. Discussion

Burn injury is a preventable injury, but when they do occur, they can leave a devastating impact on the individual and or family members. The most common cause of burn injury in our study was flame. This is similar to earlier report by Ademola et al.[4] as well as the global trend of burn injury [24]. These injuries can be modulated by adequate first aid given within the first 3 h of burn injury.

The exact components of burn first aid vary from guideline to guideline. But there is a consensus on the role of cool running water over the burn and coverage with clean wrap or cling film [7,13,15]. However, some guidelines advocate for the inclusion of any other liquid such as Aloe vera and hydrogel in the absence of water, other guidelines frowns

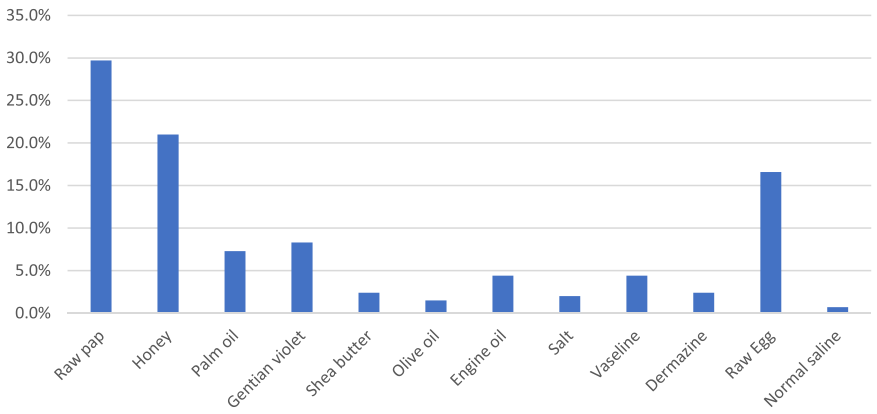

Fig. 3. Other agents used for first aid either alone or in combination. Readily available agents such as raw pap, honey and raw egg are the more commonly used agents.

Table 1
Basic characteristics of patients and duration of water application. Those that had water applied for only extinguishing flame were older and had larger burn area.

Variables		Only to extinguish flame	5 minutes	10 minutes	20 minutes	More than 20 minutes
Age (Years) *Median*		35	6	21	19	1*
Gender	Male, n (%)	14(48.3)	42(53.8)	12(63.2)	4(50)	0(0)
	Female, n (%)	15(51.7)	36(46.2)	7(36.8)	4(50)	1(100)
TBSA (%) *Median*		40 %	13.5 %	13 %	29.5 %	14 %**

**TBSA, not median TBSA
* age in years, not median age

Table 2
The effect of duration and source of water application on burn injury outcome measures. The rates of infection and mortality were lower in those that had water applied for 5 min.

Variables	5 minutes	10 minutes	20 minutes	Only to extinguish flame	**X^2 value**	P value
Infection rate	43.7 %	64.7 %	62.5 %	77.8 %	11.390	0.023* *
Increased LOS*	37.9 %	50.0 %	100.0 %	37.5 %	12.868	0.012* *
Mortality rate	9.6 %	21.4 %	12.5 %	56.5 %	33.801	0.001* *
	Running tap water	Clean water from a container	Just any water around	Unsure source of water		
Infection rate	37.5 %	49.0 %	69.6 %	70.0 %	8.620	0.041* *
Increased LOS*	56.0 %	43.9 %	52.9 %	33.3 %	2.538	0.468
Mortality rate	12.5 %	17.9 %	23.5 %	47.5 %	23.213	0.006* *

** Statistically significant
* LOS- length of hospital stay

Table 3
Regression analysis showing the effect of clean source of water and duration of water application on outcome of burn injuries.

Water applied for 5 minutes compared with more than 5 minutes	**Unstandardized β**	**Standardized β**	T-Test Value	P-Value	95 % CI Lower boundary	95 % CI Upper boundary
Reduced Infection rate	0.163	0.187	2.125	0.03 * *	0.011	0.314
Reduced LOS*	0.003	0.092	0.940	0.34	0.004	0.010
Reduced Mortality rate	0.098	0.232	2.357	0.02 * *	0.015	0.181
Clean source of water compared with unsure source						
Reduced Infection rate	0.127	0.269	2.750	0.007 * *	0.035	0.219
Reduced LOS*	0.002	0.052	0.533	0.595	0.006	0.010
Reduced Mortality rate	0.216	0.223	2.563	0.012 * *	0.049	0.383

** Statistically significant
* LOS- length of hospital stay

at application of any other substance over the wound during first aid [7, 13,15,25]. The use of analgesics for pain relief is also another important first aid component [13,15].

Our study showed that majority of the burn victims had one form of first aid or the other, with water (53.2 %) applied over the burn being the most common form of first aid. Other agents such as pap, honey, and raw eggs were applied in the remaining cases. Although the burn awareness by the Nigerian burn injury society discourages application of other agents aside from water, the persistence of these agents shows that the message may not have circulated sufficiently in the communities or is yet to be imbibed by majority of the populace. The prevalence of first aid (80.2 %) as well as use of water (53.2 %) for first aid in this study is remarkably higher than the 41.1 % and 8.9 % respectively reported by Abubakar et al. [5] from central Nigeria. It is also higher than the 51 % (overall first aid) and 10.2 % (water as first aid) reported by Olaitan et al. [19] from eastern Nigeria. Olaitan et al. [19] reported the use of

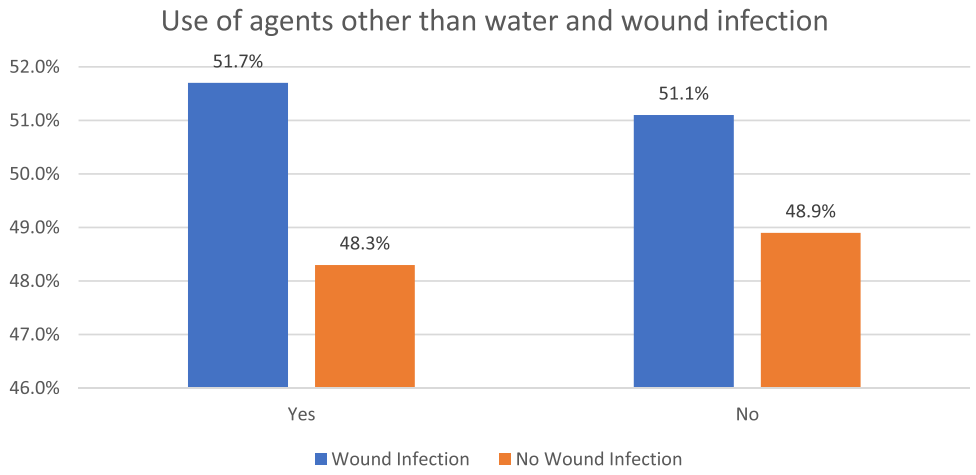

Fig. 4. The use of agents other than water over burn wound and the rate of wound infection. The rate of infection is similar among those that used other agents over the burn wound. $X^2 = 0.008$, $p = 0.930$.

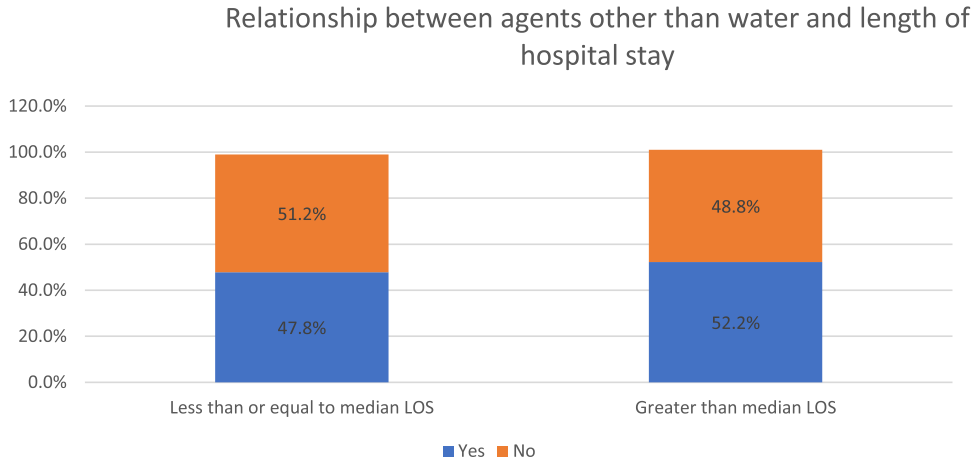

Fig. 5. Impact of agents other than water applied over burn wounds on length of hospital. There is no significant difference in length of hospital stay between those that had these agents applied and those that didn't. $X^2 = 0.167$, $p = 0.683$.

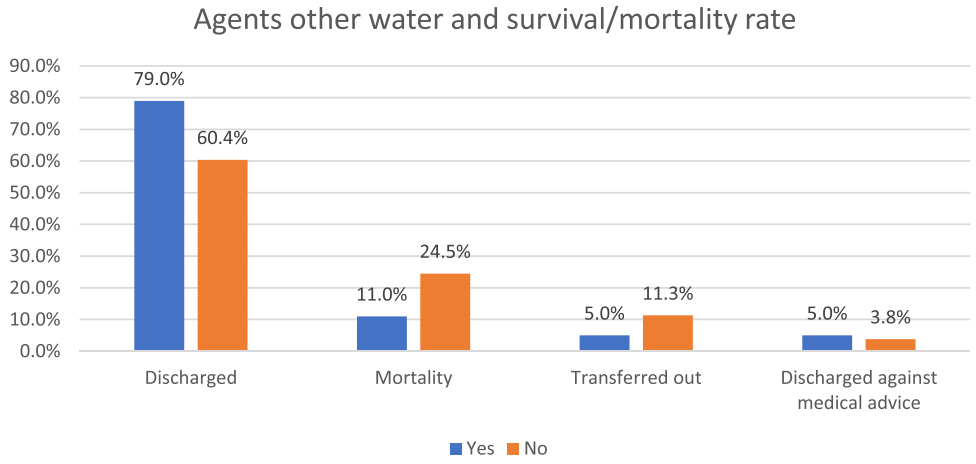

Fig. 6. Agent other than water and survival/mortality rate. There is no statistically significant difference between the groups. $X^2 = 7.736$, $p = 0.052$.

raw eggs as the commonest form of first aid, and this was corroborated by a multicenter study in eastern Nigeria by Nduagubam et al. [26]

The higher prevalence of first aid measures as well as the use of water for first aid reported in our study in comparison to other Nigerian study might be attributed to the relatively high enlightenment level of the first aid givers. Additionally, the annual burn awareness week from the center usually incorporates mass communication through the radio and television as adjuncts to market, schools, and public places of worship. This campaign would have been valuable in providing the level of awareness for the first aid givers. The finding therefore shows an

improvement in the uptake of burn first aid in our subregion. This offers hope of further improvement in burn injury first aid with intensified efforts by the burn injury societies.

Our result is however lower than the 71.9 % that received cool running water as first aid reported by Frear et al. [14] from Australia. Griffin et al. [27] in another Australian study reported that 90.6 % received running water as first aid, with 71.3 % receiving it for the recommended duration of 20 min. There is therefore a need to persist in awareness campaign to increase the knowledge about adequate burn first aid, and enhance the compliance following burn injuries in our region. No victim received any form of analgesic as first aid. This might be due to the absence of a functioning paramedic system in our country, with first aid largely given by family members. There is therefore a need to incorporate use of analgesic in to subsequent awareness campaign, as pain control has been shown to be a factor in burn first aid compliance [16].

The study found the use of cool running water, especially from the tap was significantly associated with lower mortality rate, shorter length of hospital stay, and lower rate of wound infection. These benefits reduced as the duration of water use increased above 5 min, and as the source of water becomes unsure. The finding is similar to the reduced length of hospital stay reported by Wood et al. [28] Harish et al. [29] reported a reduction in mortality with adequate water first aid in an Australian study. However, unlike the above studies from Australia where adequate cooling was for at least 20 min, the benefits from our study occurred with water use at not more than 5 min. Additionally, those who had water for extinguishing flame only or for 20 min or more had larger burn surface area greater than 20 %. The reason for the lost benefits at cooling duration at more than 5 min compared with the Australian studies might be due to the possible effect of hypothermia with prolonged use of water for first aid especially with larger area burn [30]. Hypothermia has been noted to increase burn mortality and the risk of burn infection [31,32]. The occurrence of hypothermia correlates positively with TBSA, with larger TBSA at increased risk of hypothermia and its effects [31]. This might be the basis for the 5 min recommendation, as well as minor burn categorization for the use of running water by the American Burn Association guideline [13]. Contrary to the findings from this study, the Australian studies that demonstrated beneficial effects of cool running water at a duration of 20 min had median TBSA of 1.9–5.5 % compared to the median TBSA of 20.5 % [28,29]. Therefore, in the Nigerian context where burn extents are larger than in the developed countries, water application of no more than 5 min will be more beneficial. These benefits might be due to maximizing the cooling effect of water on the burn wound while reducing hypothermia and its systemic effect on the patient. Therefore, larger surface area burn should have cool running water over the burn area for about 5 min, since using water below this duration (such as for extinguishing flame only) or above 5 min diminishes the benefit of water first aid for large surface area burn frequently encountered in our sub-region.

While some guidelines recommend the use of other agents over the wound, others discourage it because of the risk of infection, and increasing the burn process by trapping the heat energy from the burn [7,13,15]. Our study shows that though a number of other agents were applied as first aid measures, there was no statistically significant impact of these agents on burn wound infection, length of hospital stay, and mortality rate. This is contrary to the higher rate of infection reported by Olaitan et al. [19] Perhaps the low prevalence of water for first aid could have contributed to their findings compared to our study. Further prospective studies are needed to clarify if indeed the use of these other agents increases burn wound infection.

These agents continue to be used despite the repeated efforts during burn awareness campaign to discourage their use. Perhaps, the persistence of their use might be due to their availability and ease of access in homes and roadsides. Another reason might be experience of those who sustained burn injury and had silver sulfadiazine or honey used for wound care during the hospital treatment. Though unable to understand at what point some of these wound care agents are used, they continue to assume they are beneficial at all times. This underscores the need for more campaign efforts to improve understanding and role of proper burn first aid.

The limitation of this study is the non-inclusion of first aid knowledge source for the administrators of first aid. This would have enhanced the subsequent awareness campaign, and also enabled us to access the actual impact of these campaigns. Additionally, we were unable to assess the barriers to proper first aid measures among those who didn't receive adequate first aid. The adminstration of water was done by the first aid givers prior to presentation in the burn unit, therefore the study utilized reported duration of water application by the first aid givers. However, the data was collected at the time of admission into the burn unit, therefore it wasn't biased by the outcome which was measured during the course of inpatient care in the burn unit. All patients received the same standard of care as per unit protocol regardless of duration of application reported in the prehospital setting. The application of the first aid measures by trained paramedics and a prospective study designed to obviate the above limitations will be invaluable.

5. Recommendations for future research

We recommend a replication of this study in the other geopolitical zones of Nigeria. A similar result obtained in the other regions will help in the formulation of national guideline for burn injury first aid by the Nigerian Burn Injury Society. We also recommend further research into factors influencing the duration of water application by the relatives following burn injuries.

The exact TBSA at which water application for more than 5 min is no longer beneficial should be a focus of further studies. This might be easier with uptake of the 5 min topical application advocacy in burn awareness campaign.

Another area of further research is the evaluation of the impact of these first aid practices on burn depth. This should take into consideration the knowledge of first aid, the source of first aid information, the duration of first aid, and the component of first aid given.

Lastly, we recommend further study on the effect of duration of water application in burns of varying TBSA on outcomes. This will help elucidate the impact of duration of application. It will also obviate the effect of TBSA in any given water application category.

6. Clinical implications for health managers and policy makers

Formulation of a national guideline for burn injury first aid. A national guideline will aid burn education and improve burn injury outcomes. It will also lead to standardization of first aid protocols and enhance research measures.

This study demonstrates the need to provide access to clean tap water. This will make this water source easily available for use following burn injury and thereby improving burn injury outcomes.

7. Conclusion

There is a fair prevalence of burn first aid in western Nigeria, with the use of cool water, honey, raw pap, raw egg among the components of first aid. The use of cool running water (tap water, and clean container) for a period of 5 min was associated with reduced rate of wound infection, shorter length of hospital stay, and reduced mortality rate. Clean and cool water should be utilized for burn first aid over a period of 5 min before transfer to the burn center. Burn awareness campaign should focus on the topical application of water for 5 min while minimizing hypothermia. It should also discourage the use of other agents since there is no demonstrable beneficial effect of these agents on outcome. There is also a need for the government to provide access to clean tap water which has been found to be beneficial in improving the outcome of burn injuries.

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Authors' contribution

O.A Olawoye: Conceptualization- Lead; Methodology- Lead; Validation- Equal; Investigation- Lead; Resources- Equal; Data curation- Equal; Writing (Original draft)- Equal; Writing (Review & Editing)- Equal; Supervision- Lead; Project administration- Lead, **C.P Isamah:** Methodology- Equal; Software- Lead; Formal analysis- Lead; Resources- Equal; Data curation- Equal; Writing (Original draft)- Lead; Writing (Review & Editing)- Lead, **S.A Ademola:** Conceptualization- Equal; Methodology-Equal; Validation- Lead; Investigation- Equal; Writing (Original draft)- Equal; Visualization- Equal, **A.O Iyun:** Methodology-Equal; Validation-Equal; Data curation- Equal; Writing (Original draft)-Equal, **A.I Michael:** Conceptualization- Equal; Methodology-Equal; Data curation- Equal; Visualization- Lead; Investigation- Equal; Resources- Equal; Writing (Original draft)- Equal, **R.O Aderibigbe:** Conceptualization- Equal; Methodology- Equal; Data curation- Equal; Writing (Original draft)- Equal, **O.M Oluwatosin:** Conceptualization-Equal; Validation- Equal; Writing (Original draft)- Equal; Writing (Review & Editing)- Equal; Project administration- Equal; Visualization-Equal.

Declaration of Competing Interest

The authors have no conflict of interest to declare concerning this work. There are no competing interests that could have influenced the outcome of this study.

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