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Original Article

Efficacy of 2% Lignocaine Medicated Pad for Pain Alleviation during Rabies Immunoglobulin Administration: A Randomized Controlled Trial

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Abstract

Background: Rabies immunoglobulin (RIG) for animal bite victims is usually administered around the wound without the use of any anesthetic. Theoretically, the topical use of 2% lignocaine can reduce the pain during the procedure. **Objectives:** This study aimed to determine the efficacy of 2% lignocaine medicated pad (LMP) for reducing pain during administration of RIG. **Methods:** A randomized triple-blind controlled trial was done in a tertiary care setting in Kerala, India. The proximal and distal wounds of the patient with minimum two, Category III animal bite wounds were randomized to intervention and placebo arms, based on a previously generated random number sequence. Sterile gauze pads soaked with 2% lignocaine and normal saline were the intervention and placebo, respectively. Pain was the primary outcome measure and was assessed using numeric rating scale (NRS) and sound, eye, and motor pain (SEM) scale. The patient, outcome assessor, and statistician were blinded. **Results:** The wound sites and size of 100 intervention and 100 control wounds were comparable. The score of all elements of the SEM, total SEM, and NRS score were significantly lower in the wounds, which were given LMP compared to the control wounds. The number needed to treat for satisfactory pain relief and immediate pain relief was 25 and 14, respectively. No serious or minor adverse events were reported in the trial. **Conclusions:** The use of a proven drug in a topical route optimizes pain reduction from iatrogenic cause for millions of animal bite victims around the world with very little additional financial burden.

Key words: Animal bite, immunoglobulins, lignocaine, pain, rabies

Introduction

Rabies, a viral encephalitis, is caused by an RNA virus of genus: *Lyssavirus* and family: *Rhabdoviridae* and is 100% fatal till today. In India, it is estimated that 17.4 million animal bites occur annually resulting in 20,000 deaths due to human rabies. This constitutes about 36% of the total human rabies death globally.[1] The animal bites are now categorized based on the WHO guidelines for initiation of postexposure prophylaxis. Category III exposure is considered as severe and includes single or multiple transdermal bites or scratches, licks on broken skin, and contamination of mucous membrane with saliva which mandates the administration of rabies immunoglobulin (RIG) along with antirabies vaccine. With the use of the WHO categorization, exposures requiring RIG are more common nowadays. Improved availability of RIG in hospitals has also facilitated its increased use whenever indicated. The calculated dose of RIG should be infiltrated into and around all the wounds as much as feasible anatomically. Administration of RIG into and around the wound is however a painful procedure.

Theoretically, the topical use of 2% lignocaine should be able to reduce pain of patients during the administration of RIG.

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However, there are no studies that have established the efficacy of topical local anesthetic like 2% lignocaine, in reducing pain during administration of RIG locally. This study (Pain Alleviation during Immuno Globulin Trail - PAIG trial) was done to determine the efficacy of 2% lignocaine medicated pad (LMP) for reducing pain in patients during administration of RIG.

Materials and Methods

A randomized control trial, in which the patient, outcome assessor, and statistician were blinded, was conducted at the preventive clinic of a tertiary care hospital in Kerala, India. Adult patients above 18 years of age coming to the preventive clinic with Category III animal bites, in which Equine RIG was prescribed, were recruited into the study. Persons with minimum two or more wounds separated by at least 5 cm at the same site or two different sites were recruited. Those who did not give consent, those with known allergies to lignocaine, those with history of contact dermatitis, and those with any contraindications to lignocaine were excluded. All patients with mucosal exposures to animal bites were also excluded [Figure 1]. In cases where there were more than two wounds, the most proximal and distal wounds were taken for the study. Proximal wound was the wound closest to head and distal wound the one farthest from the head. In case of a wound on the face, proximity to an imaginary line drawn through the middle of the nose was considered for selection of proximal and distant wounds.

A difference of 5 points in the pain score in the intervention and control arm in the scale used as primary outcome measure was expected. This and other values required for imputation in the formula of sample size calculation were obtained from a pilot study in the clinic. The sample size was derived as 100 in each arm using the formula[2] $n = (z\,\alpha^2 + z\beta^2)\,\sigma^2/(\mu - \mu_0)^2$.

$\sigma = (n_1 - 1)\,s_1^2 + (n_2 - 1)\,s_2^2/(n_1 + n_2 - 2)$,

Where $s_1 = 4$, $s_2 = 3$

μ (pain score in placebo arm)-9

μ_0 (pain score in intervention arm)-4

n_1 and n_2-11.

Since the intervention and control wounds were in the same patients, a total of 100 patients finally participated in the study during December 2017 to March 2018.

A standard operating procedures' manual was prepared. Using this, all the staff involved in the study were trained and certified. All forms and procedures were pretested. Monthly performance monitoring reports and supervisory visits were used for the assessment of quality of work and adherence to the protocol.

Privacy was ensured during the procedure, with a family member allowed to be with the patient if so desired. Injections were administered by a single person (health inspector of

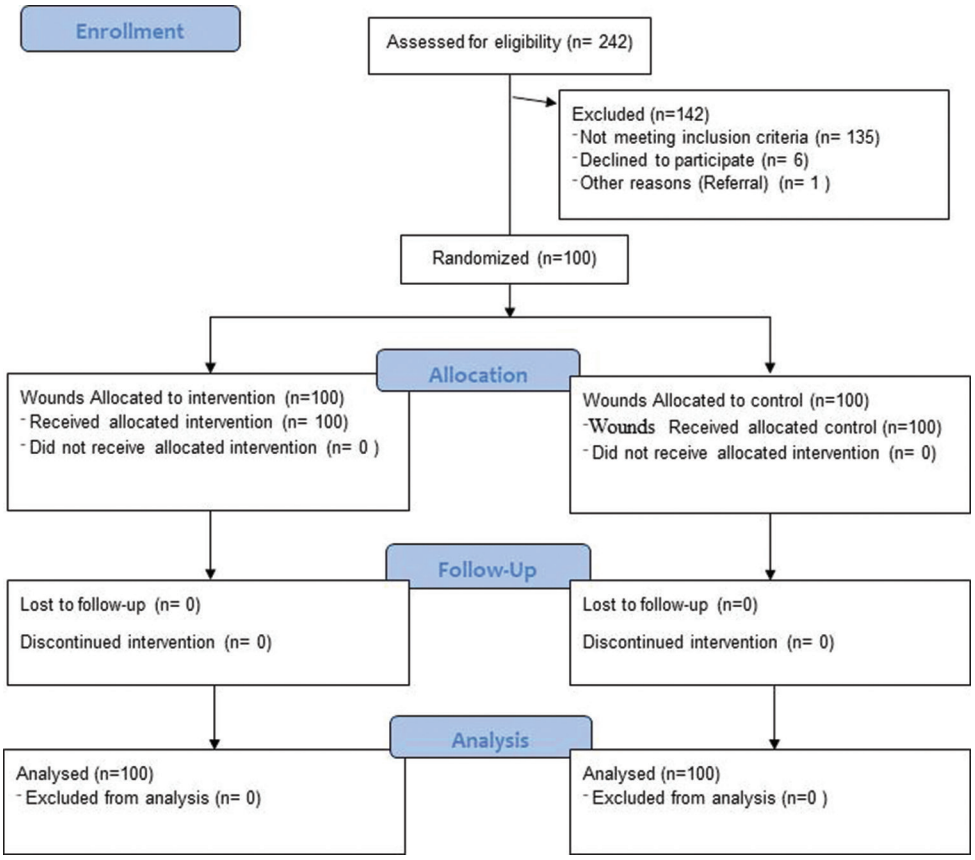

Figure 1: Consort flow diagram.

vaccination clinic) to achieve consistency in the procedures. The person was always supervised by qualified medical practitioner. The number of recruitments was restricted to the first two eligible participants per day to ensure quality of data collection. RIG was administered according the national guidelines.[1]

The procedure was done after administering the test dose of ERIG, to allow at least 20 min of contact with the local anesthetic. Patient was requested to lie in bed, in supine or prone position, depending on the site of wound. Sterile cotton pad was placed over the wound site to cover the wound. Lignocaine was instilled over the pads till the wet appearance was seen over the entire pads placed. The maximum volume of lignocaine used was 5 ml. The pad was securely plastered/bandaged according to the site. Normal saline was used as placebo on one of the wounds. It was taken in the same type of syringe and the same volume as the intervention was instilled. The intervention and placebo were given by the same person.

Blinding, randomization, and concealment of randomization

The intervention and the placebo were kept in previously labeled bottles. The labeling was done as A and B according to a previously generated coding sequence, by a team different from the investigating team. A was administered on the proximal wound and B was administered on the distal wound of the person. The person administering the intervention and placebo was not aware of the codes. The patient also was not informed which is the medication.

The proximal and distal wound of the patient was randomized to the intervention and placebo arm, based on a previously generated randomization sequence from R software (R version 4.0.3- R Core Team. R: A language and environment for statistical computing. Vienna, Austria). The proximal wound was termed as Wound A and the distal as Wound B for all patients. The randomization sequence determined whether a particular study participant is receiving the intervention or placebo on Wound A/B. While one participant may be receiving intervention in the proximal Wound A, the next person has an equal probability of receiving intervention/placebo on Wound A. In this manner, the dermatomal differences and all other unknown factors influencing the gradient of pain at different locations have been accounted for.

The patient, outcome assessor, and statistician were blinded. The allocation sequence was adequately concealed using serially numbered opaque blinded envelopes. The blinding index has not been calculated in this study.

Here, block randomization was not required because at any point, we would have equal number of intervention and control, since each patient has an intervention and control element. Furthermore, stratification was not required, because all characteristics of intervention and control were the same except the site and size of wound since each person served as his/her own control.

The randomization and the identity of A and B were written on opaque-sealed envelopes which were sequentially numbered (SNOSE) and kept with the investigator and opened by the investigator prior to withdrawal of intervention/placebo.

Outcome measures and analysis

Pain was the primary outcome measure, assessed using two scales. Numeric rating scale (NRS) was used to assess the patient's pain perception. It was rated from one to ten. The pain responses of the patients were also observed by the investigators and recorded using the sound, eye, and motor pain (SEM) scale used by Wright *et al*.[3] SEM pain scores were rated from 1–4. The effectiveness of intervention was also assessed by perceived satisfactory pain relief and time to pain relief. Other study variables included site of wound and size of wound, besides age, sex, education, occupation, and other baseline variables.

An intention to treat (ITT) analysis was planned to be done as primary analysis. Per protocol (PP) analysis also was planned if required. However, since we did not have a loss to follow-up, ITT was carried out. The difference between the pain score in the two arms was tested for significance using Wilcoxon signed-rank test. Satisfactory pain relief and time to achievement of satisfactory pain relief were compared using McNemar's test. Since each patient is his/her own control, no comparison of baseline variables was done. They have been described in percentages. Other variables that are likely to affect the pain score, namely site and size of wound, were compared in both groups, using McNemar–Bowker test.[4] Two interim analyses were planned when the sample size reached 25 and 50 in each arm. The significance level was fixed *a priori* as 0.04, as per the O-Brien Flemming[5] method. Since we did not get significance at the level of two interim analyses and no adverse events were reported, we continued till the required sample size was attained.

Institutional research committee and human ethics committee clearance were obtained before the start of the study (IEC No. 09/15/2017/MCT dated September 28, 2017). Written informed consent was taken from the study participants. The trial has been registered with the Clinical Trials Registry - India (CTRI/2018/02/011803) and is done in accordance with Good Clinical Practice guidelines. No funds were obtained for the conduct of the study.

Results

Sixty-nine men and 31 women were recruited. Among the participants, 24% were <40 years, 46% were 40–59, and 30% were elderly. The mean age of the study participants was 49.58 years (SD – 15.64). Minimum age was 18 and maximum 80 years.

62% of participants had higher than high school education including 14% graduates and postgraduates. 36% of the study participants were unemployed. 83% of the study participants belonged to the moderate level of economic category (economic status was classified according to the color coding of the public distribution system card).

Ninety-four percent of wounds were due to dog and 6% due to cat. While 54% were from domestic animals, 45% from stray and 1% wild animals, 40% among them were provoked attacks. Thirteen percent of wounds were from suspect rabid animals, which showed abnormal behavior at time of bite. The number of bleeding wounds ranged from 2 (since at least two wounds was one eligibility criteria) to 10 wounds. 35% had two, 26% had three, 16% four, 10% five, 7% six, and 2 had ten wounds. One each had 7, 9, 12, and 14 wounds. None gave a definite history of mucosal exposures.

The most common site of wound was the upper limbs in intervention (hand – 32, forearm – 18, and arm – one) and the control (hand – 28, forearm – 18, and arm – one). The next common site was lower limb [Table 1]. The wound sites in the intervention and control arm were comparable (McNemar–Bowker test value – 4.00, df – 5, and $P = 0.55$). The wounds in the intervention and the control arm were comparable in length (median 2 cm [IQR: 2] vs. 2 cm [IQR: 1.00]; Wilcoxon signed-rank test done and $P = 0.468$) and breadth (median 1.0 [IQR: 1.7] vs. 1.0 [0.65]; Wilcoxon signed-rank test done and $P = 0.482$).

The distribution of the score components of SEM in the intervention and control arm is shown in Table 2. It is seen that while administering RIG in the wounds where LMP was used, the total SEM scores were lower. Although the difference in distribution of the NRS scores is not so marked compared to the total SEM scores, we see that there is a higher number of persons with pain scores above 4 in the control wounds compared to intervention.

The mean quantity of 2% lignocaine/normal saline required for covering the wound was 2.7 ml (SD-1.02), with a range of 1–4 ml, depending on the size of wound.

The scores of all elements of the SEM score, total SEM score, and NRS were significantly lower in the wounds which were given LMP compared to the control wounds [Table 2]. Comparison was done using the Wilcoxon signed-rank test since the distribution of scores was not normal (Kolmogorov-Smirnov test done and $P < 0.05$). This shows that LMP is effective in reducing pain during RIG administration. The mean scores are displayed in Table 2 to show that it was higher for all elements of pain score in the control arm.

Number needed to treat (NNT) for satisfactory pain relief was obtained as 25 and NNT for immediate pain relief was 14 [Table 3].

No serious or minor adverse events were reported in the trial.

Table 1: Comparison of wound sites in the intervention and control arms*

	Wound site control				Total	*P*
	Face	Lower limb	Others	Upper limb		
Wound site intervention						
Face	2	1	0	1	4	0.55*
Lower limb	0	41	0	3	44	
Others	0	1	0	0	1	
Upper limb	1	6	1	43	51	
Total	3	49	1	47	200	

*McNemar–Bowker test (value-4.00, df-5)

Discussion

Measurement of pain and pain relief is a difficult challenge since pain is a very complex subjective experience. Many one-dimensional scales (numerical rating scale, visual analog scale) and multidimensional scales (short-form McGill questionnaire, brief pain inventory short form) are available. Besides behavioral scales like the SEM scale and objective markers like skin conductivity, heart rate and neurological markers also exist. Although there are many accepted tools, there does not exist a valid and reliable method of quantifying one's experience of pain. Hence, we have used two scales, namely the NRS and the SEM for outcome measurement in our study.[6]

In our study, we got statistically significant reduction in pain during RIG administration to the wounds with application of 2% LMP, compared to placebo. It is suggested that a 30% reduction in pain can be considered as clinically significant.[7] Here, the difference in the mean NRS score is minimal (6%; calculated as difference of 0.3/4.5 × 100), for total motor pain score also, this is minimal 12% (0.7/5.7 × 100) or median score difference is 1/6 × 100 = 16%. Since pain is an iatrogenic harm of injection, even small mitigation benefits may be considered to be clinically significant.[8]

1%–2% lignocaine has been used effectively in several other procedures like suturing and skin harvest.[9-11] Its potency is related to lipophilicity[12] and its mechanism of action is well documented.[13-15] Topical anesthetics have proven efficacy, as demonstrated by multiple studies testing for anesthesia effect with various painful stimuli, including venipuncture,[16] pin-prick testing,[17] and split-thickness skin graft donation.[18] Fear of needles and pain can cause anxiety in patients awaiting procedures in the outpatient setting.[19,20] Application of topical anesthetic before or in place of injection of local anesthetic can help relieve anxiety as well.

Even if a person does not have a high pain score, minimal suffering is also significant and worth providing relief for. This is especially so because the cost of the process in terms of manpower material and money is very low. The cost of material has been worked out to be only Rs. 5 and Rs. 17 for human resource, making a total cost of Rs. 22 (US $0.31).

The guideline for pain mitigation recommends intervention on any five main domains of pain management, namely procedural, physical, pharmacologic, psychological, and process. This is called the "5 P" approach.[8] In this study, we have studied the pharmacologic intervention. The procedural,

Table 2: Scores compared in the intervention and control arm

Distribution of SEM scores in intervention and control arm			
During RIG administration	**Pain score**	**Intervention wound (*n*=100)**	**Control wound (*n*=100)**
Sound score	1	47	23
	2	38	59
	3	13	17
	4	2	1
Eye score	1	31	23
	2	59	59
	3	9	17
	4	1	1
Motor score	1	49	12
	2	46	76
	3	5	12

Efficacy of LMP: Comparison of SEM and NRS scores				
During RIG administration	**Mean (SD)**		**Difference between means (95%CI)**	***P***
	Intervention wound	**Control wound**		
Sound score	1.70 (0.77)	1.96 (0.67)	0.26 (0.06-0.46)	0.003*
Eye score	1.80 (0.64)	2.00 (0.49)	0.20 (0.04-0.36)	0.007*
Motor score	1.56 (0.59)	1.78 (0.58)	0.22 (0.06-0.38)	0.003*
Total score of SEM	5.08 (1.66)	5.72 (1.30)	0.64 (0.22-1.06)	0.000*
NRS score	4.20 (1.35)	4.48 (1.36)	0.28 (0.09-0.65)	0.002*

*Wilcoxon signed rank test. SEM: Standard error of mean, RIG: Rabies immunoglobulin, LMP: Lignocaine medicated pad, NRS: Numeric rating scale. SD: Standard deviation, CI: Confidence interval

Table 3: Comparison of perceived satisfactory and immediate pain relief in intervention and control arms and number needed to treat

Perceived satisfactory pain relief						
Intervention arm	**Control arm**		**Incidence of satisfactory pain relief**		**ARR (Incidence if satisfactory pain relief among intervention arm-Incidence of satisfactory pain relief among control arm)**	**NNT (1/ARR)**
	Pain relieved	**Pain not relieved**	**Intervention arm**	**Control arm**		
Pain relieved	90	5	0.95	0.91	0.04	25
Pain not relieved	1	4				

Immediate pain relief						
Intervention arm	**Control arm**		**Incidence of immediate pain relief**		**ARR incidence of immediate pain relief among intervention arm-incidence of immediate pain relief among control arm**	**NNT (1/ARR)**
	Yes	**No**	**Intervention arm**	**Control arm**		
Yes	21	13	0.34	0.27	0.07	14
No	6	60				

ARR: Absolute risk reduction, NNT: Number needed to treat

psychological, and process domains would be comparable in the two arms since the intervention was administered by the same person. The physical domain which is discussed in the paper which includes positioning and breast feeding may not be relevant in this context.

Pain relief during immunization has been studied.[21] This is the first trial-based attempt in pain relief during RIG administration. Its use can be expanded to other indications for immunoglobulin administration also. Most pharmacological interventions for topical anesthesia involve ready-to-use lignocaine or prilocaine ointments. It is for the first time that a study is being done using an anesthetic medicated pad.

The pressure pain threshold would be different based on the types of tissues involved in the injury. This is the reason for analyzing the significance of differences in site and size of wounds across the two arms using the McNemar–Bowker test. This difference was not significant. There could have been interferences of pain of the wound with the pain during injecting RIG. The objective of the study was to assess

the analgesic effect of LMP during RIG administration. It may have reduced the pain of the wound also. These were not separately assessed. The possible interferences of pain perception due to other factors like number of wounds would be equal in the intervention and control arm since it was in the same individual. This methodology is the strength of the study.

Conclusions

The study shows that LMP is effective for reducing pain during RIG administration. The intervention is cheap, cost-effective, requires no special training, easily replicable even in primary care settings, and with no adverse effects. Similar trials need to be done in adults in other geographic areas to bring about consistency in results. The usefulness of the procedure in alleviating pain in children and during other immunoglobulin administrations needs to be studied. Any remote effects of the medication on immunity also need to be looked into. This study is one step forward toward working for, if not a pain free society, optimizing pain relief, especially from iatrogenic cause. It is also an attempt to improve the quality of care given to patients seeking antirabies prophylaxis.

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Conflicts of interest

There are no conflicts of interest.

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