

Topical lidocaine-ibuprofen versus lidocaine-prilocaine as a Local Anesthetic Agent in Reducing Central Venous Catheter Insertion Pain: a Randomized Controlled Trial

[Reza Azizkhani](#)¹, [Omid Ghayour Najafabadi](#)¹, [Farhad Heydari](#)¹, [Mina Saber](#)², [Sarah Mousavi](#)³

¹Department of Emergency Medicine, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

²Department of Dermatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

³Department of Clinical Pharmacy and Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

Objective: This study was performed to evaluate the effectiveness of topical lidocaine-ibuprofen combination compared to lidocaine-prilocaine combination (Xyla-P) in reduction of the pain during central venous catheter (CVC) insertion.

Methods: In this randomized clinical trial, 100 adult patients requiring CVC insertion in the emergency department (ED) were enrolled. These patients were divided randomly into two groups. The site of CVC insertion was covered with topical Xyla-P cream (2 g) in the first group, and topical lidocaine-ibuprofen (2 g) cream in the second group. The primary outcome was assessment of pain during CVC implantation. The secondary outcomes were physician's satisfaction and the incidence of side effects.

Results: The mean age was 41.67 ± 9.66 years (range 18–61), and 36% of patients were female. The mean VAS pain score during CVC insertion was 4.61 ± 2.05 in the LP group and 3.86 ± 2.09 in the LI group, respectively (mean difference of 0.75 [95% confidence interval (CI): -0.80 to 1.56]), The mean VAS pain score during lidocaine injection was 1.78 ± 0.79 in the LP group and 1.52 ± 0.79 in the LI group, respectively (mean difference of 0.26 [95% CI: -0.05 to 0.57]), The physician's satisfaction did not show statistically significant differences between two groups.

Conclusion: This study showed that topical lidocaine-ibuprofen is as effective as Xyla-P in relieving acute pain during CVC insertion.

Keywords: Ibuprofen, Emergency department, Lidocaine, Central Venous Catheter, Pain

Short Title in English: Lidocaine-Ibuprofen as a Local Anesthetic

Introduction

Central venous catheter (CVC) insertion as well as many other procedures in the emergency department (ED) can be associated with pain, anxiety, and discomfort, and these were often reduced with the use of local anesthetics such as lidocaine (1). Therefore, CVC insertion should

be considered as a frequent and painful procedure in ED that requires serious pain management. Local anesthesia reduces the procedural pain, however the injection of local anesthesia is usually painful itself (1, 2). Also, even after the establishment of effective local anesthesia, subsequent procedural steps like using the locator needle, anchoring the central venous catheter to the skin, or the eventual catheter tunneling were a source of pain and distress (2, 3). Most clinicians believe that the first injection of local anesthesia at the cannulation site will give maximum pain stimulus compared to subsequent steps (3).

Various analgesic methods were used to reduce or prevent procedural pain. Intravenous analgesics is an effective therapeutic option during invasive percutaneous procedures, however, in many patients, it is not possible due to clinical conditions and lack of facilities. An alternative approach is to use topical anesthesia for percutaneous procedures (4, 5). This is an available, low-cost, and effective method. There is good evidence that adults benefit from reducing discomfort and anxiety by using an effective topical analgesic cream at the site of the procedure (4-6).

The best topical anesthetic agents have long been the center of controversy. The use of the local anesthetic compound is associated with several disadvantages, such as pin-prick pain at the site of lidocaine infiltration, blanching of the skin, and vasoconstriction (5, 7). The Xyla-P cream 5% (2.5% lidocaine and 2.5% prilocaine) has been shown to effectively reduce pain associated with needle punctures (5, 6, 8). Topical nonsteroidal anti-inflammatory drugs (NSAID), such as transdermal diclofenac patch (TDP) and ibuprofen gel by their capacity to inhibit prostaglandin synthesis are expected to provide analgesia and decrease the inflammatory response to cannulation (6, 7, 9).

The major route of elimination of lidocaine and prilocaine is through hepatic metabolism, and metabolites are excreted by the kidneys. Maximum plasma concentrations were reached after

approximately 1.5-3 hours. The required application period of EMLA may vary depending on the location of treatment. EMLA has been shown to be effective on the face and thighs after as little as 25 minutes (10). Ibuprofen is rapidly absorbed, has renal excretion, and has a short plasma elimination half-life of 2.5 ± 1.4 hours, with a number-needed-to-treat (NNT) value of 3.9. It is completely eliminated in 24 hours after the last dose (11,12). Pain relief after ibuprofen gel application was 25 minutes (9).

Ibuprofen gel has high clinical efficacy in the treatment of acute musculoskeletal pain in adults (9). Also lidocaine and ibuprofen have a synergistic analgesic effect (12). Park et al. found that the application of lidocaine-ibuprofen to the skin of rats had significant local anesthetic effects as determined by two different tests and that this effect was significantly greater and with faster onset compared with the commercial product, Xyla-P (12).

To our knowledge, the combination of topical lidocaine-ibuprofen has not been evaluated to reduce the pain of procedures in the ED. This study aimed to evaluate the effectiveness of topical lidocaine-ibuprofen combination compared to the Xyla-P cream in reduction of the pain during CVC insertion.

Materials and methods

Study design and setting:

This prospective randomized double-blind clinical trial was conducted in the ED of two university teaching hospitals (Alzahraand KashaniHospital) in Isfahan, Iran. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.703). The trial was registered in the Iranian Registry of Clinical Trials under the number IRCT20180129038549N10. Written consent for participation and an agreement for data to be stored and processed only for research purposes was obtained from participants.

Study population

All adult patients requiring CVC insertion in the ED were evaluated for eligibility for the study. Patients were included in the study if they were older than 18 years, awake, alert, and oriented, and had a stable medical condition. Patients with visual, mental, or verbal disorders, a history of an allergic reaction to local anesthetics, a history of favism, methemoglobin, renal and liver disease, skin diseases at or around the CVC insertion site, a history of drug addiction, a history of analgesic use within 24 hours before the procedure were excluded. Also, patients were excluded if the venous catheter placement was not successful the first time (skin puncture was repeated more than once). All enrolled patients consented to participate in the study.

Intervention

The patients based on a random-allocation software package (Random Allocation Software 2.0) were randomly divided into two groups to receive one of the two topical anesthetics: Xyla-P cream (lidocaine 2.5% and prilocaine 2.5%), or lidocaine-ibuprofen cream (lidocaine 2% and ibuprofen 5%).

In the first group (LP group), the researchers applied 2 gr of Xyla-P cream (Tehran Chemie Pharmaceutical Company, Iran) at the CVC insertion site. In the second group (LI group), the researchers applied 2 g of a fixed-dose combination containing 5% ibuprofen (SobhanDarou Company, Iran) and 2% lidocaine (SinaDarou Company, Iran) cream at the site of CVC insertion.

The topical anesthetic was applied on a 5*5 cm surface area over the procedure site in a thick layer and covered with a transparent patch 30 min before the CVC insertion (11).

Lidocaine-ibuprofen cream was prepared in 30 g weighted tubes in collaboration with the Faculty of Pharmacology (Isfahan University of Medical Sciences). It was matched in terms of color, smell, and shape with the Xyla-P cream. An independent investigator who was not involved in

clinical management and data collection did the randomization and prepared topical creams every day and named them with the codes A and B.

After 30 min (10-13), the skin site was cleaned with topical detergents, and 5 ml of 2% lidocaine was injected through a 25-gauge needle. The blinded investigator injected 3 mL of lidocaine directly superficial to the internal jugular vein, then injected 1 mL just to the left and 1 mL just to the right of the vein for anchoring stitches (1). Five minutes after injection, an attempt was made to CVC insertion into the right internal jugular vein using the anterior approach. All CVC insertions were carried out under ultrasound guidance. Each patient received a 7 Fr triple-lumen catheter via a non-tunneled approach.

Outcomes and data collection

The patient's self-assessment of pain was elicited using a standardized approach and recorded on a Visual Analog Scale (VAS). The scale consisted of a 100 mm horizontal line; the left end of the scale (0) represented "no pain" and the right end (100) "worst possible pain". The patient was asked to indicate pain intensity along horizontal line, and this rating was then measured from the left edge (5). The physician's satisfaction was assessed using a 10-point verbal numeric rating scale from 0 (completely dissatisfied) to 10 (completely satisfied).

The patient's assessment of pain was recorded after initial subcutaneous lidocaine injection, and just after CVC insertion. The physician's satisfaction was recorded after the overall procedure was completed. At the beginning of the study, patient characteristics (age, sex, and body mass index (BMI)) were recorded. In addition, the observer-rated local side effects (erythema, edema, pruritus, and blanching) during the study. Heart rate, systolic and diastolic blood pressure, and peripheral oxygen saturation were continuously monitored and recorded before intervention and after CVC insertion. All measurements were collected by investigators blinded to randomization and the type

of topical analgesia used. The patients, physicians as well as nurses who participated in the trial were blinded to the randomization.

The primary outcome of the study was pain during CVC insertion. The secondary outcomes were physician satisfaction and the incidence of side effects.

Sample size

In each group, 45 patients were required at 95% confidence level, power of 80%, and the standard deviation of pain scores in the two groups equal to 2.49 and 2.27, and the error level of 1.69 (resulting from the difference between the mean of pain scores in the two groups) regarding the previous studies (14). Thus, the study population of 50 patients per group was calculated for an anticipated dropout rate of 10% to ensure an adequately powered study.

Statistical Analysis

Finally, the collected data was analyzed using SPSS software (ver. 25) and they were shown as Mean \pm standard deviation (SD) or frequency (%). Chi-square test was used to compare qualitative data between the two groups, independent t-test and paired t-test were used to compare the mean of quantitative data, and univariate analysis was used to compare the mean pain score by adjusting confounding factors, such as age, sex, and BMI. The significance level was. A P less than 0.05 was considered significant.

Results:

In this study, 121 patients were eligible for the study, of which 21 were excluded and finally 100 patients were included in the analysis (Figure 1). The mean age was 41.67 ± 9.66 years (range 18–61), and 36% of patients were female. There was no statistically significant difference in baseline characteristics between the two groups (Table 1).

The mean VAS pain score during CVC insertion was 4.61 ± 2.05 in the LP group and 3.86 ± 2.09 in the LI group, respectively, with a mean difference of 0.75 [95% confidence interval (CI): -0.80 to 1.56], The mean VAS pain score during lidocaine injection was 1.78 ± 0.79 in the LP group and 1.52 ± 0.79 in the LI group, respectively, with a mean difference of 0.26 [95% CI: -0.05 to 0.57], The physician's satisfaction did not show statistically significant differences between two groups (Table 2).

The occurrence of erythema and edema with Xyla-P or with lidocaine-ibuprofen cream was not different. Three subjects exhibited blanching with Xyla-P and none in the LI group. blanching was significantly lower in the LI group (Table 2). Also, there was no significant difference in vital signs between the LI and LP groups before and after the CVC insertion ($p > 0.05$) (Table 3).

Discussion

Procedural pain relief or control not only reduces anxiety and fear in patients but also increases their cooperation and contributing to the ease of the procedure and improves overall patient satisfaction. Although only a small number of topical agents are available for use in peripheral and local conditions, there is growing evidence to support the effectiveness of such preparations for the relief of procedural pain.

Previous studies showed pain and discomfort during CVC insertion (1-3). Puntillo et al. found a big positive surge in mean pain score during CVC insertion than the pre-procedural pain (15).

There are several ways to reduce pain and anxiety, one of which is the use of local anesthesia. Local anesthesia reduces the procedural pain, however the injection of local anesthesia itself is usually painful. Therefore, topical anesthetic agents are used to reduce injection pain.

The results of the current study demonstrated administration of either topical Xyla-P or lidocaine-ibuprofen combination can effectively reduce pain during CVC insertion. The systemic effects of both creams were similar.

As stated earlier, we could find no studies directly evaluating the topical lidocaine-ibuprofen combination in reducing acute procedural pain. However, in a study by Park et al., they applied lidocaine-ibuprofen ionic liquid to the skin of rats to assess its absorption. They investigated that the use of lidocaine-ibuprofen on the skin of rats had significant local anesthetic effects as determined by two different experiments and that this effect was significantly greater and with faster onset compared with the commercial product, eutectic mixture of local anesthetics (EMLA). In addition, there were no adverse side effects observed in the rats or their skin (12). Also in another study, The Lidocaine-Ibuprofen ionic liquid was studied for its local anesthetic effect in rats. The results of local anesthetic effect confirmed that the time for onset of action by Lidocaine-Ibuprofen ionic liquid was significantly higher than that for EMLA. However, a tactile test showed the stronger and faster local anesthetic effect of Lidocaine-Ibuprofen ionic liquid when compared to that of EMLA (16).

The randomized crossover trial showed that there was no significant analgesic difference between EMLA cream and 5% lidocaine cream. Both creams were effective without clinically serious side effects (15). This finding is similar to our findings. Several studies exist about topical ibuprofen used successfully in treating the pain associated with musculoskeletal injuries. Therefore, we compared our results to the aforementioned articles. Previous studies have evaluated the effect of topical use of ibuprofen (such as gels, patches, and foam dressings cream) compared with oral administration of ibuprofen, and showed significant pain reduction in musculoskeletal injuries, osteoarthritis, persistent venous leg ulcer pain, and venipuncture (17-20). Trnavský et al. showed

that ibuprofen cream exhibits good efficacy and safety in the treatment of knee osteoarthritis (18). Whitefield et al. suggested 5% ibuprofen gel has comparable efficacy to 400 mg oral ibuprofen thrice daily for the treatment of acute pain following musculoskeletal injuries (21).

Topically NSAIDs are effective in decreasing acute and chronic pain by inhibiting prostaglandin synthesis at the site of application (19,20). A recent review of topical NSAIDs reported that ibuprofen gel demonstrated high clinical efficacy in the treatment of acute musculoskeletal pain in adults (21). Wade et al. showed that ibuprofen gel was associated with effective pain relief in the treatment of acute musculoskeletal injuries, and had a median time to significant pain relief of fewer than 30 minutes (9).

Although the effect of the combination of ibuprofen plus lidocaine has not yet been investigated, the combination of other NSAIDs plus lidocaine has been evaluated. Azizkhani et al. found that topical lidocaine-diclofenac was as effective as lidocaine-prilocaine in relieving acute pain during CVC insertion (22). Linares-Gil et al. demonstrated that topical formulation containing lidocaine plus diclofenac be safe and more effective than the topical lidocaine alone for a reduction in pain intensity in the three first post-surgery days in benign anorectal surgery (23). Lidocaine and NSAIDs have a synergistic analgesic effect (23,24). Ibuprofen increases the absorption of lidocaine into the skin and therefore can make this topical anesthetic work faster and better (12).

The present study showed that a combination of lidocaine plus ibuprofen had a similar analgesic effect compared to Xyla-P. However, since ibuprofen gel is more cost-effective than other analgesic creams such as Xyla-P, this combination can be considered. Further studies on different conditions and different percentages of ibuprofen and lidocaine are recommended.

The vasoconstrictive effect of Xyla-P might be responsible for blanching, and vasodilation that occurs after this effect disappears may lead to erythema and edema (7). Consistent with the present

study, topical ibuprofen had only infrequent side effects, such as mild and completely reversible skin reactions (18). The potential advantage of topical lidocaine-ibuprofen is the minimization of both local and systemic side effects.

Limitations:

First, small sample size and evaluation of pain severity by a subjective method (VAS) can be considered as limitations of the present study. Second, there was no placebo group for the comparison of VAS score during lidocaine injection. Third, a minimum duration of 30 min was used to evaluate the effect of both creams, which is a relatively long period in ED, while most studies have shown that topical EMLAs and NSAIDs require 30-60 minutes for full effect. Fourth, the skin thickness affects topical absorption of the drug, so further studies can assess this more accurately. Finally, Likert Type Verbal Scale was not considered in this study, it can be used in the further studies. It is also suggested to do future studies to evaluate the effect of the present drug combination at different times and in different procedures to generalize the results of the present study to the community with more certainty.

Conclusion

This study showed that topical lidocaine-ibuprofen is as effective as Xyla-P in relieving acute pain during CVC insertion. Although, the pain score in lidocaine-ibuprofen cream was lower than Xyla-P although the difference was not statically significant. Also, lidocaine-ibuprofen combination cream is more cost-effective than Xyla-P cream.

Declarations

Acknowledgments

The present article was extracted from the thesis by Dr. Omid Ghayour to achieve her specialist degree in emergency medicine from Isfahan University of Medical Sciences. The authors would like to express their gratitude to the staff of the ED of Al-Zahra and Kashani Hospitals, Isfahan, Iran.

Ethics Committee Approval:

The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.703).

Informed Consent:

Oral and written informed consent was obtained from all parents, before enrolment into the study.

Peer-review:

Externally peer-reviewed.

Authorship Contributions:

Concept, study design, and data collection and evaluation: R.A., O.G., F.H., S.M., and M.S., Statistical analysis, and interpretation of data. R.A., F.H., and O.G., Literature Search: F.H., R.A., S.M., O.G., and M.S., Drafted the manuscript: F.H. and R.A., and O.G. All authors edited and approved the final version of this paper for submission, and also participated in the finalization of the manuscript and approved the final draft.

Conflict of Interest:

The authors declare no conflict of interest.

Funding and supports

This study was funded by Isfahan University of Medical Sciences.

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Table 1: Basic characteristics of patients in two groups

Variables	LP group (n=50)	LI group (n=50)	P value
Sex (no. (%))			0.485
Male	34(68.0)	30(60.0)	
Female	16(32.0)	20(40.0)	
Age (year)	41.13 ± 3.69	32.12 ± 3.68	0.292
BMI (kg/m²)	28.58 ± 2.41	28.43 ± 2.39	0.710

LP: Lidocaine-Prilocaine; LI: Lidocaine-Ibuprofen

Data are presented as mean ± standard deviation unless otherwise indicated.

Table 2: Comparison of pain scores, discomfort score and side effects in two groups

Variables	Groups		Difference (95% confidence interval)
	LP group (n=50)	LI group (n=50)	
Pain (based on VAS)			
During lidocaine injection	1.78 ± 0.79	1.52 ± 0.79	0.26 (-0.05 to 0.57)
During CVC insertion	4.61 ± 2.05	3.86 ± 2.09	0.75 (-0.08 to 1.56)
Physician satisfaction	6.58 ± 1.89	7.12 ± 1.97	0.54 (-0.22 to 1.30)
Side effects (no. (%))			
Erythema	2(4.0)	1(2.0)	2 (-4.7 to 8.7)
Edema	1(2.0)	1(2.0)	0 (-2.8 to 2.8)
Blanching	3(6.0)	0(0.0)	6 (2.6 to 9.4)

LP: Lidocaine-Prilocaine; LI: Lidocaine-Ibuprofen; CVC: central venous catheter VAS: visual analogue scale

Data are presented as mean ± standard deviation unless otherwise indicated.

Table 3: Comparison of vital signs before and after central venous c insertion

Variables	Groups	Vital Signs		P value
		Before Intervention	After Catheterization	
Systolic Blood Pressure	LP group	125.87 ± 16.18	123.33 ± 15.92	0.367
	LI group	124.18 ± 14.65	124.66 ± 15.65	0.765
Diastolic Blood Pressure	LP group	80.71 ± 9.89	81.15 ± 10.03	0.214
	LI group	80.49 ± 10.16	82.15 ± 10.01	0.198
Heart Rate	LP group	83.18 ± 11.86	85.18 ± 12.14	0.148
	LI group	82.81 ± 10.89	84.78 ± 11.32	0.232

LP: Lidocaine-Prilocaine; LI: Lidocaine-Ibuprofen

Data are presented as mean ± standard deviation unless otherwise indicated.

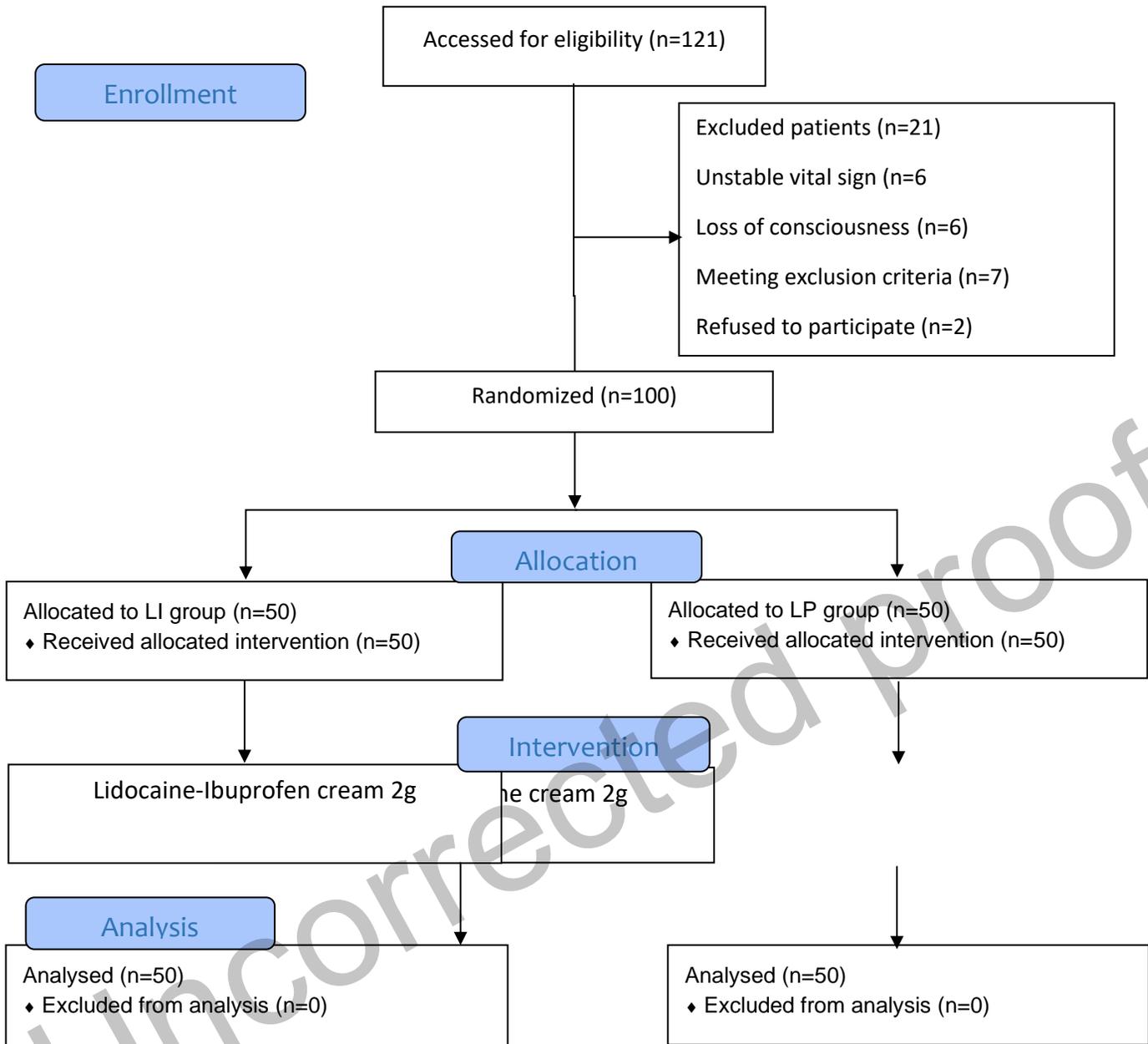


Fig. 1. CONSORT flow diagram of the study