

Comparative Evaluation of Efficacy of Transdermal Diclofenac Patch, Eutectic Mixture of Local Anaesthetic Cream and Placebo for Venous Cannulation Pain and Attenuation of Hemodynamic Response

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Abstract: ***Purpose-**Venous cannulation is painful and associated with a high incidence of vasovagal and pressor responses. The aim of this study is to evaluate the efficacy of transdermal diclofenac patch (TDP) and eutectic mixture of local anaesthetics (EMLA) cream for intravenous cannulation pain and to attenuate the haemodynamic response to it. **Methods-** This was a prospective, randomized, double blind, placebo controlled study in which 102 adult ASA I and II patients undergoing elective surgery of both sexes were divided into three groups. Group P received placebo cream, Group E received EMLA cream – 2gm/10cm² and Group D received TDP – 100mg/50cm², at the proposed site, 60min prior to the insertion of a 18G IV cannula. The resulting pain was assessed by VAS. The heart rate and blood pressure was recorded before and at 1min of Intravenous cannulation to assess the stress response. **Results-**TDP and EMLA cream were effective in reducing both the incidence and severity of pain in comparison to the placebo group and also attenuated the stress response to it. **Conclusion:** TDP can be used as an alternative to EMLA cream for reducing the incidence and severity of venous cannulation pain and for attenuating the haemodynamic response, in patients who are sensitive to EMLA cream.*

Keywords: Transdermal Diclofenac Patch, Eutectic mixture of local anaesthetics cream, Intravenous cannulation, Haemodynamic stress response.

1. Introduction

Pain is a complex matrix of biological, psychological and sociological phenomenon causing discomfort and anxiety [1] - [3] which can lead to a vasovagal reaction [4] and pressor responses [5]. Various methods have been employed to alleviate pain and anxiety by venous cannulation [6] like ethyl chloride spray [7], intradermal or subcutaneous injection of lignocaine [8] and distraction techniques [9] - [13]. Awareness of increasing importance of patient comfort in terms of quality of care has led to the recommendations of providing topical analgesia for venous cannulation for children and adults. Topical application of EMLA cream is one of the most popular methods of reducing venous cannulation pain, but is associated with blanching of the skin which may interfere with the procedure. TDP has been utilized for topical pain relief in osteoarthritis, musculoskeletal pain [14] - [15] and for post operative analgesia [16].

2. Methods

A prospective, randomized, double blind, placebo controlled study was carried out. 102 adults of both sexes in ASA I and II physical status, between the age group of 18-80yrs, who were posted for elective surgery, were included in this study. Institutional Ethical Committee approval and written informed consent was obtained. They were divided into three groups. Group P - Placebo, Group E - EMLA and Group D – TDP.

The exclusion criteria were;

- Known sensitivity to local anesthetics
- Allergic to NSAIDS
- Skin lesions at the site of venous cannulation
- Late pregnancy
- History of analgesic intake with in previous 24 hrs

In the preoperative visit, the patients were examined and investigated appropriately. Informed consent was obtained and patients were educated about reporting pain on the 11 point Visual Analogue Scale (VAS 0-10) where 0 = no pain and 10 = worst imaginable pain. Severity of VAS score (1-3 mild pain, 4-6 moderate pain and 7-10 severe pain) was explained to them and the patients were asked to mark the line to indicate the pain intensity. The site of IV cannulation on the dorsum of the hand or forearm was selected and the part was shaved. In the preoperative room they were divided randomly into 3 groups. Patients in Group P received lubricating gel, Group E patients received a thick layer of EMLA cream (Prilox, Neon -2gm/10cm²) which contains 2.5% lignocaine and 2.5% prilocaine, and Group D patients received TDP of 100mg with an absorption area of 50cm² (Nupatch 100, Zydus cadilla); and all three were covered by the occlusive dressing. They were applied 60min [17] prior to venous cannulation at the proposed site on the non dominant hand. After marking the boundary of the area of patch/cream/gel they were removed and cleaned with spirit. A senior anesthesiologist who was blinded for all the three groups and not a part of the study was the investigator. Under aseptic precautions, intravenous cannulation was

performed with a 18G cannula. Heart rate, systolic, diastolic and mean arterial blood pressure were recorded before and at 1 min of intravenous cannulation. Patients whose vein could not be cannulated successfully in the first attempt were considered as cannulation failure. The patients were asked to mark the line to indicate the pain intensity with VAS [18].

3. Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level. Analysis of variance (ANOVA) has been used to find the significance of study parameters between the three groups. Post-hoc Tukey test has been used to find the pair wise significance, Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within the group and Chi-square/ Fisher Exact test has been used to find the significance of study parameters on a categorical scale between the three groups.

Significant figures:

- + Suggestive significance (P value: 0.05<P<0.10)
- * Moderately significant (P value: 0.01<P \leq 0.05)
- ** Strongly significant (P value: P \leq 0.01)

Statistical software: SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

4. Results

A total of 102 patients were inducted into the study. Due to failure of cannulation in the 1st attempt, 12 patients had to be excluded from statistical analysis, leaving 30 in each group. In this study all the three groups were comparable with respect to demographic characteristics (Table 1).

Table 1: Age and Sex Distribution

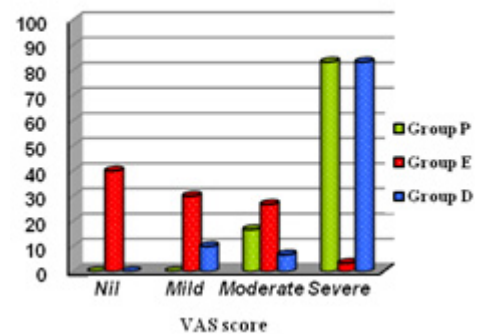
	Group P	Group E	Group D	p value
Age (yrs)	45.27 \pm 13.01	45.66 \pm 14.57	45.70 \pm 12.09	0.990
Sex M:F	12:18	15:15	13:17	0.730

In Group D & P, no patients came in VAS score of 0 but 12 patients (40%) in Group E had VAS score of 0. VAS score (1-3) was found in 9 patients of Group E (30%) and 3 patients of Group D (10%) but 0 patient in Group P. VAS score (4-6) was found in 8 patients of Group E (26.7%), 2 patients of Group D (6.7%) and 5 patients of Group P (16.7%). VAS score (7-10) was seen in 1 patient of Group E (3.3%) and 25 patients (83.3%) in Group D and equal number in Group P (Table 2 & Chart 1).

Table 2: Comparison of VAS score

VAS score	Group P		Group E		Group D	
	No	%	No	%	No	%
Nil	0	0.0	12	40.0	0	0.0
Mild	0	0.0	9	30.0	3	10.0
Moderate	5	16.7	8	26.7	2	6.7
Severe	25	83.3	1	3.3	25	83.3
Total	30	100.0	30	100.0	30	100.0

Chart 1

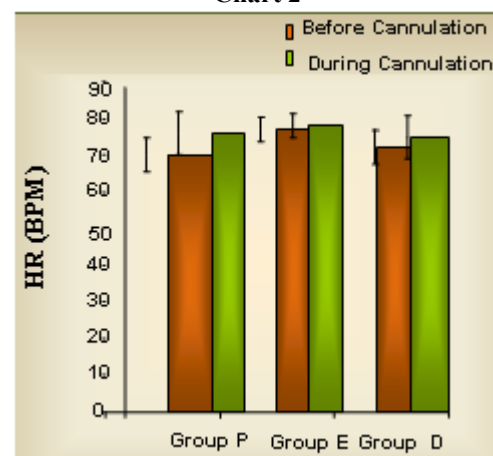


There was an increase in heart rate (HR) from baseline in all the three groups at 1 min of IV cannulation, which was statistically strongly significant in Group P, moderately significant in Group D and not significant in Group E (Table 3 and Chart 2).

Table 3: Comparison of HR

HR (bpm)	Group P	Group E	Group D
Before Cannulation	70.00 \pm 4.68	77.00 \pm 3.30	72.00 \pm 4.68
At 1min cannulation	75.90 \pm 5.83	78.00 \pm 3.31	74.90 \pm 5.83
Difference	5.9	1	2.9
p value	<0.001** strongly significant	0.544 Not significant	0.035* Moderately significant

Chart 2

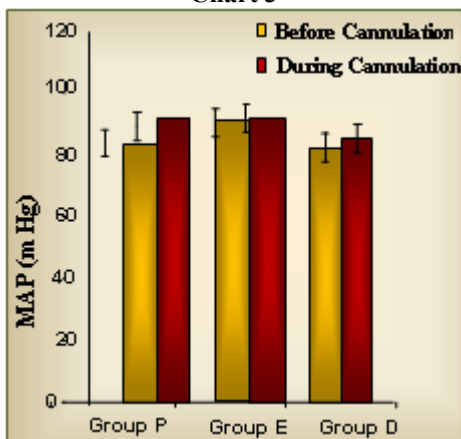


Mean arterial pressure (MAP) in Group P before and at 1min of IV cannulation was 83.6 \pm 4.5 and 89.4 \pm 4.6 respectively. In Group E it was 90.3 \pm 4.6 and 91.9 \pm 4.3 respectively. In Group D it was 82.10 \pm 4.6 and 85.2 \pm 4.8 respectively with p <0.001. Clinically the difference was less in Group E (1.60) and Group D (3.07), but was statistically significant (Table 4 and Chart 3).

Table 4: Comparison of Mean Arterial Pressure

MAP(mm Hg)	Group P	Group E	Group D
Before cannulation	83.67±4.51	90.33±4.56	82.10±4.60
At 1 min cannulation	89.40±4.58	91.93±4.31	85.17±4.78
Difference	5.73	1.6	3.07
p value	<0.001**	<0.001**	<0.001**

Chart 3



5. Discussion

Venous cannulation, the most commonly performed invasive procedure in hospital patient is painful and associated with high incidence of vasovagal reactions and pressor responses. A few patients develop needle phobia and avoid medical care. In order to alleviate pain and anxiety and improve the patient comfort, we have tried to evaluate whether TDP has any local analgesic effect for intravenous cannulation in comparison to EMLA cream and a lubricating gel. It is already been well established by many studies that EMLA cream [19] - [20] is very effective as a topical anaesthetic for various procedures and decreases the stress response [21] and vasovagal reaction. But it is associated with localized vasoconstriction [22] - [23] which prevents successful cannulation and carries a rare risk of methaemoglobinemia.

Topical NSAIDS show therapeutic efficacy by inhibiting the activity of cyclo-oxygenase which is necessary for the biosynthesis of a pain inducer- prostaglandin [24] - [25] at the site of application, thus decreasing the inflammatory response to cannulation and reducing the incidence of peripheral vein thrombophlebitis [26]. They also offer the advantage of enhanced and sustained local drug delivery to the affected tissues with a low incidence of adverse systemic effects. In our study, we found that pain intensity is decreased during cannulation with TDP as shown by VAS score and decreased haemodynamic stress response but was not superior to EMLA cream. This is also similar to another study of C.M. Deshpande [27]. Anil Agarwal et al [28], [29] showed that TDP and EMLA cream are equally effective in decreasing the incidence and severity of venous cannulation pain. Amitash Dutta et al [30] found piroxicam gel (NSAID) does not significantly reduce pain during IV cannulation but it may reduce inflammation in the post cannulation site and the chances of peripheral vein thrombophlebitis. TDP is not as effective as EMLA cream, because diclofenac acts by inhibiting the mediators of the inflammatory response to injury and not when applied to non-inflamed surfaces. The penetration of TDP, at least after single dose is not predictable and may strongly be influenced by individual

skin properties [31]. The limitations are – EMLA and TDP have to be applied for a minimum of 60min before intravenous cannulation and this may not be feasible in all the patients. Cost factor may also be a constraint in poor patients.

6. Conclusion

TDP is effective in reducing both the incidence and severity of venous cannulation pain but is not superior to EMLA cream in producing local analgesic effect. It overcomes the side effects of EMLA cream leading to skin blanching as a result of localized vasoconstriction, which prevents successful cannulation and has the risk of methaemoglobinemia. So TDP can be used as an alternative for pain relief during intravenous cannulation and for decreasing the chances of peripheral thrombophlebitis.

7. Future Implications

It can be used to treat short-term pain due to minor strains, sprains, bruises and for pre-emptive postoperative analgesia with better patient compliance. For post-traumatic pain increased strength of the diclofenac is required in the patch which requires larger sample and further clinical trials.

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