

Evaluation of Novel Cooling Gel Sheets for Antipyretic Effect

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Received: 7th Dec, 17; Revised: 27th Jan, 18, Accepted: 4th Feb, 18; Available Online: 25th Feb, 2018

ABSTRACT

Rationale: Fever is basically rise in body temperature above normal. Fever itself is not a disease but it is an indication that the body is trying to fight an illness or an infection. Fever is usually associated with physical discomfort, and most people feel better when the fever is treated. But depending on age, physical condition, and the underlying cause, the patient may or may not require medical treatment for the fever alone. In some cases it is not recommended to treat fever as the rise in temperature is important to kill the viruses and bacteria. These are the causes of the infection but rise in the temperature heats up the body and causes discomfort. There are various approaches to cool the body from the outside without treating the cause of the fever. They include lukewarm or cool wraps or baths, cold drinks and very light clothing. Using a wet cloth on the forehead is an age old remedy for treating fever but the problem with this method is that the cloth needs to be changed after every 1 or 2 minute. **Methods:** The formulations were evaluated for Clinical trials of the patches. **Conclusion:** From the present investigation it can be concluded that that C_s formulation showed optimum homogeneity, consistency, viscosity, swelling studies and stability. Cooling gel sheets could be a potential method for reducing fever in near future which can be replacements for the old method of applying wet cloth on the forehead. The cooling gel sheets could provide cooling for maximum 6-8 hrs with a single sheet.

Keywords: Aquagel, Fever, Cooling gel Sheet, Hydrogel, Temperature

INTRODUCTION

Hydrogels are highly absorbent natural or synthetic polymers which can contain over 99.9% water. The polymer chains contain acidic or basic groups bound to them¹. The acidic groups on the chains deprotonate at high pH, whereas the basic groups protonate at low pH. In the presence of an aqueous solution, the polymer chains absorb water and the association, dissociation and binding of various ions to polymer chains causes the hydrogel to swell². As the temperature raises the heat of the skin causes the evaporation of water contained within cooling gel sheet which creates a cooling sensation on the surface of the skin.

MATERIALS AND METHODS

HPMC (1 lakh cps), Carbopol 934 NF, Xanthum gum, Sodium CMC, Guar gum, Gelatin, Sodium polyacrylate, HPC (Hydroxyl propyl cellulose), Methacrylic acid, Ultraze 20, Polyvinyl alcohol, Polyethylene glycol 400, Dimethicone were obtained from Unijules Life Sciences, Nagpur. All the ingredients were of analytical grade. Different formulations were formulated using different polymers like Xanthan gum, HPMC, sodium CMC, Guar gum, Gelatin. Amongst all HPMC forms the most stable gel. The gels made from other polymers were not stable. The viscosity of the gels was low and had less water absorbing capacity as compared to HPMC.

Clinical Trails

Aim of the study

To determine safety and efficacy of cooling gel sheets in the patients of mild to moderate pyrexia.

Study design

This was an open label, phase 2 clinical trial conducted at the outpatient department of SHRI BRAMHACHAITANYA AYURVEDIYA & PANCHAKARMA HOSPITAL, KARAD, Maharashtra, India. Patients of either sex aged between 0 to 50 years of age were selected for the study. Patients were evaluated by proper inclusion and exclusion criteria and who were willing to give informed consent. They were evaluated for pyrexia of primary origin. Follow up was taken after every hour up to the 8 hours. In each visit patients were assessed for symptoms score.

Materials and methods

Proper Inclusion and Exclusion criteria were decided as:

Inclusion criteria: A total of 57 patients of either sex, between 0-50 years of age were taken in which the diagnosis of pyrexia of primary origin (viral fever, infectious fever) was confirmed.

Exclusion criteria: Patients with fever higher than 103 °C and with acute complications were excluded from the trial. Pregnant and lactating women, patients with concomitant severe illness necessitating other medications, patients with severe hypertension, history of severe unstable angina, myocardial infarction, CVAs, renal failure, and those patients, who were not willing to give informed consent were also excluded from the study.

Table 1: Report Synopsis

Name of the Sponsor	UNIJULES LIFE SCIENCES LTD, NAGPUR																								
Name of the Finished Products Test Products :	“COOLING GEL SHEETS”																								
BATCH NO. :	177E001																								
Name of the Active Ingredients :	<table border="1"> <thead> <tr> <th>Sr. no.</th> <th>Ingredients</th> <th>wt. in gram</th> </tr> </thead> <tbody> <tr> <td>(1)</td> <td>Acrypol 934</td> <td>0.4 g</td> </tr> <tr> <td>(2)</td> <td>HPMC (1lakh cps)</td> <td>4 g</td> </tr> <tr> <td>(3)</td> <td>Water</td> <td>100ml</td> </tr> <tr> <td>(4)</td> <td>Poly vinyl Alcohol</td> <td>0.5 g</td> </tr> <tr> <td>(5)</td> <td>Polyethylene glycol 400</td> <td>1.5 g</td> </tr> <tr> <td>(6)</td> <td>Dimethicone</td> <td>2 g</td> </tr> <tr> <td>(7)</td> <td>Menthol(1%)</td> <td>2 ml</td> </tr> </tbody> </table>	Sr. no.	Ingredients	wt. in gram	(1)	Acrypol 934	0.4 g	(2)	HPMC (1lakh cps)	4 g	(3)	Water	100ml	(4)	Poly vinyl Alcohol	0.5 g	(5)	Polyethylene glycol 400	1.5 g	(6)	Dimethicone	2 g	(7)	Menthol(1%)	2 ml
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Title of the study :	“AN OPEN LABEL STUDY TO EVALUATE SAFETY AND EFFICACY OF COOLING GEL SHEETS IN THE PATIENTS OF PYREXIA”																								
Clinical Investigator :	Dr. S. B. Malekar SHRI BRAMHACHAITANYA AYURVEDIYA & PANCHAKARMA HOSPITAL, KARAD.																								
Study Centre	Out Patients Department SHRI BRAMHACHAITANYA AYURVEDIYA & PANCHAKARMA HOSPITAL, KARAD.																								
Objectives	To study the safety & efficacy of “COOLING GEL SHEETS” in pyrexia patients.																								
Number of subjects	57																								
Diagnosis & Criteria for inclusion	Pyrexia between 99 °C to 103 °C																								
Route of administration	Local																								

Dose & duration of treatment

Adult: This gel sheet can be applied externally as and when required, this can be applied every 4 hours or every 6 hours as per the intensity of the fever

Children: 6 hourly

No other analgesic, antipyretic was given until the patient’s symptoms were seen during the course of therapy.

Study procedure

All eligible patients were given cooling gel sheet for application on forehead every 6 hours.

All the patients were assessed for body temperature before the start of the treatment and after every 1 hour they were being assessed for body temperature. The improvement in the pyrexia was assessed using a predefined symptom score scale from 0 to 3 (0=absent, 1=mild, 2=moderate and 3=severe).

Primary and secondary efficacy parameters

Table 2: Observations of the clinical trails

Column Title	0 hr (A)	1 hr (B)	2 hr (C)	4 hr (D)	6 hr (E)	8 hr (F)
Mean	2.589285	1.410714	0.660714	0.375	0.150943	0.132075
Standard deviation (SD)	0.4964	0.6260	0.8587	0.7523	0.5334	0.5203
Sample size	56	56	56	56	53	53
Std. error of mean (SEM)	0.06634	0.08365	0.1147	0.1005	0.07326	0.07146
Lower 95% Conf. limit	2.456	1.243	0.4306	0.1734	0.003803	0.2756
Upper 95% Conf. limit	2.722	1.578	0.8908	0.5766	0.2981	0.2756
Minimum	2.000	1.000	0.000	0.000	0.000	0.000
Median (50 th percentile)	3.000	1.000	0.000	0.000	0.000	0.000
Maximum	3.000	3.000	3.000	3.000	3.000	3.000
Normality test KS	0.3852	0.4048	0.3149	0.4409	0.5171	0.5247
Normality test P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Passed normality test?	No	No	No	No	No	No

Table 3: Comparison table of the columns

Comparison	Mean Difference	q	P value
Column A vs Column B	1.179	13.630	*** P<0.001
Column A vs Column C	1.929	22.304	*** P<0.001
Column A vs Column D	2.214	25.609	*** P<0.001
Column A vs Column E	2.438	27.809	*** P<0.001
Column A vs Column F	2.457	28.024	*** P<0.001
Column B vs Column C	0.7500	8.674	*** P<0.001
Column B vs Column D	1.036	11.978	*** P<0.001
Column B vs Column E	1.260	14.368	*** P<0.001
Column B vs Column F	1.279	14.583	*** P<0.001
Column C vs Column D	0.2857	3.304	ns P>0.05
Column C vs Column E	0.5098	5.814	*** P<0.001
Column C vs Column F	0.5286	6.029	*** P<0.001
Column D vs Column E	0.2241	2.555	ns P>0.05
Column D vs Column F	0.2429	2.771	ns P>0.05
Column E vs Column F	0.01887	0.2123	ns P>0.05

Primary efficacy parameters were considered as reduction in for body temperature and symptom score assessment. Secondary efficacy parameters were reduction in the incidence of adverse events and overall compliance to the therapy.

Statistical analysis

Statistical analysis was done on the basis of intent to treat, to compare the body temperature before and after every assessment. The minimum level of significance was fixed at 95% confidence limit and a 1-sided p value of <0.05 was considered as significant.

RESULTS AND DISCUSSION

Clinical Trails

About 73 patients were screened for trial out of them 57 patients gave complete follow up.

There was significant difference observed in mean body temperature level from 2.589+/-0.496 to 0.132+/-0.520

One-way Analysis of Variance (ANOVA)

The P value is < 0.0001, considered extremely significant. Variation among column is significantly greater than expected by chance.

Tukey-Kramer Multiple Comparisons Test

If the value of q is greater than 4.061 then the P value is less than 0.05.

No adverse events were noted during the treatment as there were no significant changes observed in other symptoms. The clinical trial of cooling gel sheets observed a significant difference in the body temperature and pyrexia pattern. The patch contains menthol, which reinforces the analgesic feeling of coldness, helping to relax tense muscles in the head and neck. For instant cooling, calming relief, use with or without oral medication, whenever headache or migraine pain strike. The patch contains a high percentage of water which works with the body’s natural cooling system helping to cool the body. As the temperature rises, the heat of the skin causes the evaporation of water contained within cooling gel sheet

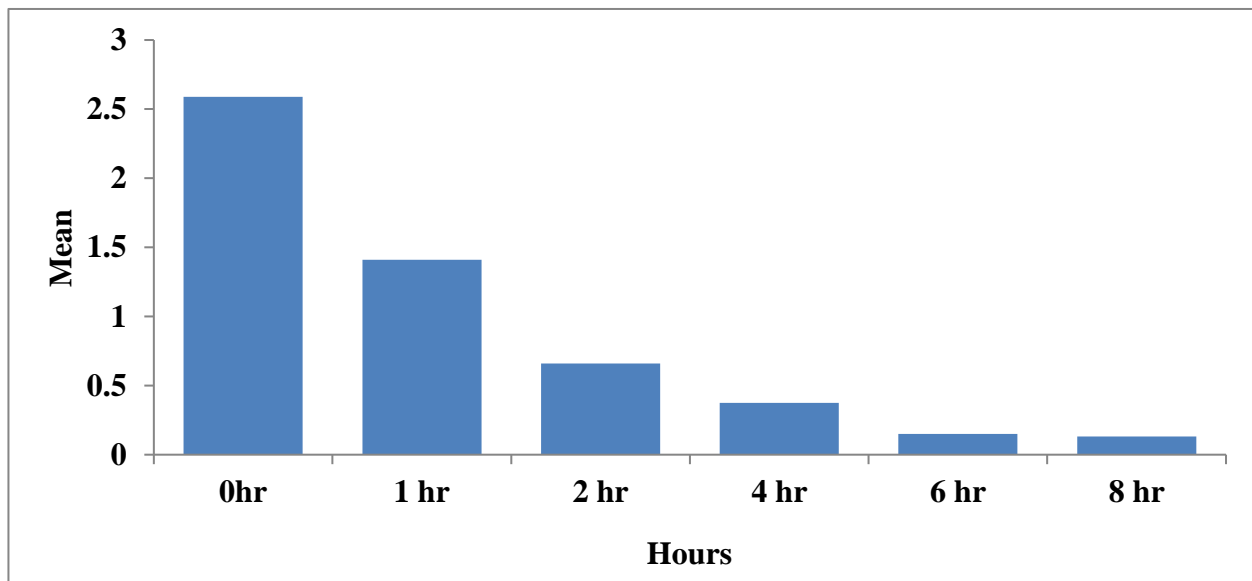


Figure 1: Improvement in the body temperature.

which creates a cooling sensation on the surface of the skin. The excellent heat transfer ability is made possible by the gels unique structure which disperses heat freely and maintains a constant and steady cooling effect that lasts up to 8 hours. TDDS is a drug delivery system in which skin is used as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation. This system of drug administration has many advantages .it bypass hepatic first pass metabolism. It maintains a constant and prolonged drug level in the body. It avoids the risk and inconvenience of i.v therapy. It does not necessitate hospitalization and close medical supervision of administration. It avoids gastrointestinal drug absorption difficulties caused by gastrointestinal pH, enzymatic activity, and drug interactions with food, drinks, or other orally administered drugs. It substitutes for oral administration of medication when that route is unsuitable, as in instances of vomiting and/or diarrhoea. It provides capacity to terminate drug effect rapidly (if clinically desired) by removal of drug application from the surface of the skin.

Failure of oral antipyretics and increasing incidences of adverse drug reactions to those drugs like acetaminophen and nimesulide etc. have caused major threat to subjects receiving this therapy especially in children and long term consumers. Liver disorders and other toxicity symptoms of these antipyretics can be avoided by use of this unconventional method i.e. TDDS. A patient of viral fever or other PUO's can be given this therapy easily rather than antipyretics without causing any systemic effects or adverse drug reactions. This study proves efficacy and safety of cooling gel sheets it helps reducing pyrexia to a significant level which can reduce the necessity of consumption of antipyretics.

CONCLUSION

The formulation C₅ contained the highest water content. This formulation does not cause any redness or abrasion so this formulation can be used as a replacement for the old method of sponging in which the cloth has to be changed after every 2 min. This patch provides cooling upto 6 hrs without any cumbersome replacements. The clinical trial of the gel sheet further showed that the gel sheet can be used in the future to reduce the fever without side effects and effectively.

ACKNOWLEDGMENT

Authors are thankful to Unijules Life Sciences Ltd, Nagpur for providing chemicals and their motivation and co-operation to carry out this research work.

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