TREATMENT OF ACUTE SOFT TISSUE TRAUMA WITH A TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUG (BIPHENYLACETIC ACID 3% GEL)

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in the treatment of acute soft tissue injuries. However, taken orally, NSAIDs have a definite incidence of gastro-intestinal toxicity. Since acute soft tissue trauma is normally localised, use of a topical NSAID may eliminate this undesirable side-effect. This study was designed to evaluate the efficacy and safety of a topical NSAID, biphenylacetic acid 3% gel (Traxam®) in the treatment of soft tissue trauma. Thirty-two patients (22 males and 10 females) with acute soft tissue trauma were enrolled at the Department of Orthopaedic Surgery, National University Hospital, Singapore from 7 June 1988 to 28 March 1989. Each patient was treated for a period of one week with bipenylacetic acid 3% gel (Traxam®), 60 mg three times a day. Statistically significant improvement was found in pain, swelling and functional impairment in all patients assessed at day 3 and day 7 after the injury. The speed of recovery was enhanced. The medication was found to be well tolerated and safe.

Keywords: Non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAID, soft tissue trauma, biphenylacetic acid 3% gel

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to be effective in a variety of inflammatory conditions. Recently, the use of NSAIDs has also been extended to the treatment of acute soft tissue injuries. These medications are usually taken orally and have been shown to have associated gastro-intestinal toxicity. As acute soft tissue trauma is usually localised, a topical medication that would act directly at the site of inflammation would enhance the symptomatic relief and greatly reduce the potential for systemic side effects. This study was designed to assess the usefulness of a topical NSAID in the treatment of soft tissue injury.

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MATERIALS AND METHODS

Patient selection

Patients with a diagnosis of acute soft tissue trauma within 48 hours of injury were eligible for this study. The candidate had to have moderate to severe pain localised to one site of any extremity. All patients in the study were X-rayed to exclude any bony fracture. The following were excluded from the study : pregnant women and nursing mothers, patients with serious medical illnesses, patients who had taken analgesic or NSAID preparations within the last week or concomitant medications likely to interfere with or mask the study drug effect, e.g. glucocorticoids, anticoagulants, anti-depressants, muscle relaxants and Quinolone antibiotics, and patients with history of allergy or skin diseases. Only patients between the ages of 18 and 55 were eligible for this study. All patients signed a patient consent form prior to enrolment.

Biphenylacetic Acid 3% Gel (BPAA)

This is a non-steroidal anti-inflammatory and analgesic drug which is an active metabolite of fenbufen (marketed under the name of Lederfen, Clinopal, Napanol and Bufemid). The gel base contains 1% polycarboxyvinyl, 3.4% diisopropanolamine, 30% absolute ethyl alcohol and 62.6% purified water.

Biphenylacetic acid 3% gel is marketed by Lederle Laboratories under the tradename of Traxam®.

Methodology

Patients were seen at day 1 (baseline), at day 3 and day 7. On day 1, the extent of the primary injury was examined and assessed by the investigators and the first dose of study medication was applied to the patient under the supervision of a staff nurse. Six centimetres of the BPAA gel (approximately 2gm, which is equivalent to 60mg of BPAA) was measured out and gently applied into the skin over the affected area. Vigorous massage with the gel was discouraged. The patient was asked to continue applying BPAA three times daily (180mg of BPAA 3% gel) for 7 days. The necessary safety laboratory tests were done at baseline which included haematological, biochemical and urinalysis. The patient was also instructed as to the proper method of completing the patient diary card. This allowed for the patient's subjective assessment of the

severity of the symptoms. The patient was then reviewed on day 3 for an evaluation of the response to treatment. Patient compliance was checked and any problems with the medication was recorded. The final visit was on day 7 when the patient's compliance and response to medication was documented. Patients were instructed to return all the tubes of the medication. These tubes were weighed and counted to assess patient compliance. Haematological, biochemical and urinalysis tests were again performed. A final diary card was completed by the patient prior to dismissal from the study. Figures 1 and 2 show the criteria for assessments (Overall Assessment of Injury and Overall Effectiveness of Treatment) by the investigator and the diary card of the patient.

Fig 1

Investigator's Assessment of Patient's Injury

	None	Mild	Moderate	Severe
Spontaneous pain*				
Pain on movement*				
Tenderness on pressure				
Functional impairment				
Spasm of surrounding musculature				
Oedema				
Haematoma/ Ecchymosis				
Erythema				

*Patient must have on score of moderate, or severe, pain to be eligible.

OVERALL ASSESSMENT OF INJURY (ALL SYMPTOMS)

NONE: ☐ MILD: ☐ MODERATE: ☐ SEVERE: ☐

OVERALL EFFECTIVENESS OF TREATMENT

NONE: ☐ SLIGHT: ☐ MODERATE: ☐

GOOD: ☐ VERY GOOD: ☐

Statistical methods/data handling

The statistical testing was performed on an "intention to treat" population which included all patients entered into the study. The analysis of response for this trial was based on the mean efficacy scores and the changes noted from baseline along with the standard errors for each of the efficacy parameters recorded. The percentages of patients showing an improvement of at least one category on the investigators' overall assessment of injury at (a) day 3 and (b) day 7 were calculated. These percentages were based on all patients treated. Patients with no improvement or who worsened, and patients who dropped out before the specified time point (day 3, day 7) for drug related reasons (lack of efficacy or toxicity) were considered treatment failures.

RESULTS

Thirty-two patients were enrolled in this study at the Department of Orthopaedic Surgery, National University Hospital, Singapore from 7 June 1988 to 28 March 1989. There were 22 males and 10 females. Among them, 26 patients

Fig 2

Patient's Self Assessment

Day 1, 3 and 7

Please complete at the time of clinic visit by placing a mark on each line to indicate how you felt the last 24 hours.

1. How severe is the pain when you are resting?
   None Severe
   0----1----2----3----4----5----6----7----8-----9---10
2. How severe is the pain when you are moving?
   None Severe
   0----1----2----3----4----5----6----7----8-----9---10
3. How much pain did you get last night?
   None Severe
   0----1----2----3----4----5----6----7----8-----9---10
4. How much does your condition interfere with your normal working activities?
   None Severe
   0----1----2----3----4----5----6----7----8-----9---10
5. How much does your condition interfere with leisure activities?
   None Severe
   0----1----2----3----4----5----6----7----8-----9---10

*How many times did you apply the gel today? _____

Did you take tablets for the pain? No ____ Yes ____

Type _____ How many taken? _____

were of Chinese descent, 4 were Black and two were Caucasians. The mean age was 29.3 years with 63% aged 30 or less. The distribution of treated sites and type of injury (bruise or sprain or both) are shown in Table I. The predominant site of soft tissue injury was the ankle. Sprains were the most common type of injury reported.

Table I

Distribution of Site by Type of Injury

Injury Site (Frequency)	Injury Classification			Total
	Sprain	Bruise	Bruise & Sprain	
Arm	1	0	0	1
Shoulder	2	0	1	3
Wrist	1	0	0	1
Ankle	16	0	6	22
Foot	0	1	1	2
Knee	2	0	0	2
Heel	1	0	0	1
Total	23	1	8	32

Efficacy analysis

The analysis of response for this study was based on the mean efficacy scores and the changes noted from baseline along with the standard error for each of the efficacy parameters recorded. As shown in Table II and Fig 3, all clinical parameters of injury showed a statistically significant improvement by the mean severity score at day 7 relative to baseline (2 tailed paired t-test). The change from the baseline to day 3 was statistically significant for all features except for "haematoma/ecchymosis". The percentage of patients recording an absence of each individual clinical feature increased from baseline to day 3 and from day 3 to day 7. On completion of the study, the overall assessment of injury as evaluated by the investigators had improved in 22 patients (69%). In another efficacy parameter of Overall Effectiveness of Treatment, 20 patients (67%) showed "good effectiveness" and 4 patients (13%) "very good" effectiveness in response to treatment. Only one patient (3%) reported effectiveness to be "slight" (see Fig 4). Table III shows the mean diary scores of the patients. Statistically significant reductions were detected in the overall diary score when day 3 was compared to baseline (-2.2 units, p-value = 0.01) and when day 7 was compared to baseline (-3.4 units, p-value = 0.0001). After 3 days of treatment, the overall diary score as assessed by the patients themselves, had improved for 31 patients (97%), one patient being not evaluable; and after 7 days of study 28 patients (88%) showed an improvement, 2 patients being unchanged and one patient did not return to the clinic for assessment.

Table II
Summary of Mean Improvement Scores by Feature Relative to Baseline

Feature	B/L Mean	St. dev	D3 Mean	P	D7 Mean	P
Functional impairment	1.6	0.7	-0.4	0.01	-0.8	0.01
Erythema	0.7	0.7	-0.4	0.01	-0.6	0.01
Spasm of surrounding musculature	1.1	0.6	-0.5	0.01	-0.8	0.01
Tenderness of pressure	2.0	0.6	-0.5	0.01	-1.0	0.01
Edema	1.6	0.8	-0.5	0.01	-1.0	0.01
Haematoma/ Ecchymosis	0.8	0.8	-0.2	0.11	-0.5	0.01
Spontaneous pain	1.7	0.7	-1.0	0.01	-1.1	0.01
Pain on movement	2.0	0.5	-0.5	0.01	-1.0	0.01

B/L - Baseline
St. dev - Standard Deviation
D3 - Day 3
P - P-value
D7 - Day 7

Safety analysis

No skin sensitivity was recorded throughout the investigation. The medication was well tolerated. There was one patient, a 19 year old Chinese male with an ankle sprain who had transient elevation of his transaminase enzymes. At baseline his SGOT was 33 iu/l (normal 5 to 40 iu/l) and the SGPT was 22 iu/l (normal 5 to 40 iu/l). At day 7 the SGOT was raised to

Fig 3. - Mean Value of Investigators' Assessment of Severity of Injury Features Throughout the Study

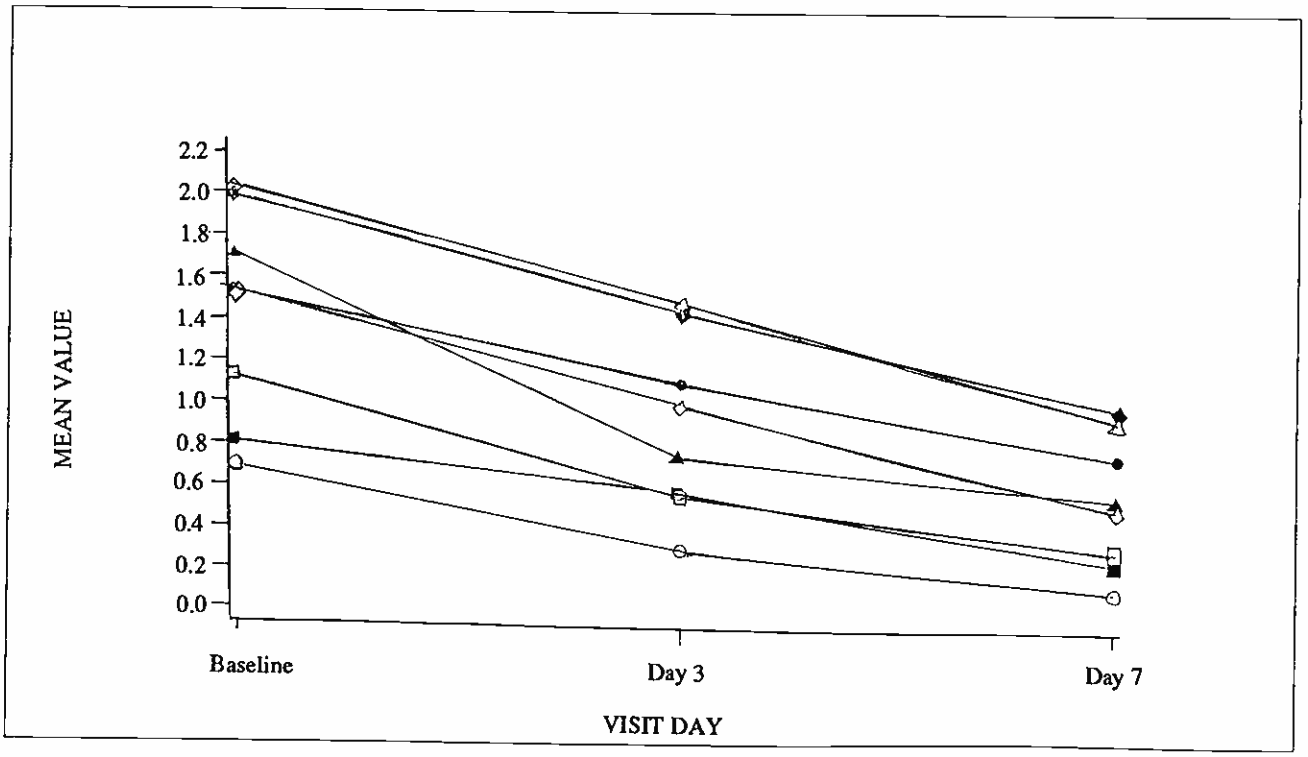

Fig 4. - Overall Effectiveness of Treatment

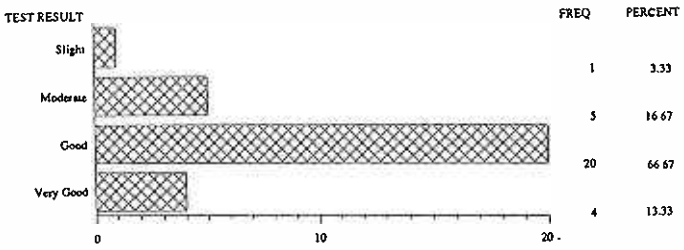

Table III
Mean Diary Scores of Patients

		Diary Answer		
		Mean	STD	N
Diary Question	Relative Day			
1	0	4.8	1.7	32
	3	2.9	1.4	32
	7	1.5	1.4	30
2	0	6.5	1.8	32
	3	3.9	1.6	32
	7	2.8	1.7	30
3	0	4.6	2.4	31
	3	2.5	1.8	32
	7	1.3	1.5	30
4	0	6.5	2.1	32
	3	4.3	2.1	32
	7	3.0	2.4	30
5	0	5.9	2.4	32
	3	4.1	2.2	32
	7	3.1	2.5	30

1 = Resting pain
2 = Pain on movement
3 = Pain last night
4 = Work activity
5 = Leisure activity
N = No of patients

171 iu/l and SGPT 209 iu/l. The laboratory examination also revealed a slight eosinophilia at 7.3% up from a baseline value of 4.9%. The patient was asymptomatic and on subsequent repeat testing, the transaminases returned to normal. A Hepatitis B antigen screen was negative.

DISCUSSION

Non-steroidal anti-inflammatory medications have been useful in reducing inflammation as well as pain in a variety of conditions. A major limitation on the use of these medications is their associated gastrointestinal toxicity. This study examined the usefulness as well as the safety of external use of a NSAID preparation (BPAA 3% gel) in patients with signs and symptoms of acute soft tissue trauma. Generally, soft tissue injury is managed by rest, elevation and analgesic support. The symptoms are usually self limiting, showing complete resolution within 2 to 3 weeks. Currently, oral preparations of NSAIDs have become more popular in the treatment of acute soft tissue injuries. The therapeutic intent is expanded beyond pure analgesia to include prompt reduction in localised oedema with an associated enhancement of the functional disability and a general reduction in the time of recovery[1]. Jakobsen et al[2] has questioned whether NSAIDs are appropriate treatment in the management of acute soft tissue injuries and has provided data from 6 placebo control studies in response. The overall conclusion from these six studies was that a one to two week treatment course with a NSAID was beneficial barring the gastrointestinal side effects. Bourne et al[3] demonstrated in his study, an improved rate of recovery using ibuprofen compared with paracetamol suggesting that the anti-inflammatory component plays a part.

Our study using BPAA 3% gel was found to be extremely well tolerated by patients and did not produce any skin reactions. The patients' overall assessment of BPAA 3% gel was that it provided good to very good analgesic support. There was statistically significant improvement in severity scores from baseline to day 3 and day 7. Although a placebo group was not used in this trial, the results compare favourably with 5 European clinical trials of BPAA 3% gel in soft tissue injury which were designed as double blind randomised placebo controlled studies. In these studies it was found that the effectiveness of BPAA 3% gel was highly statistically significant within the first week of injury[4].

There was one case of transient but reversible elevation of the transaminase enzymes in a patient with an ankle sprain. There was one similar case in BPAA soft tissue trial conducted in South Korea[5]. The patient also presented with significantly rising transaminase values observed 7 days after the initial injury. The elevated transaminase value returned to normal range spontaneously and on rechallenging with BPAA 3% gel, there were no secondary transaminase elevations.

CONCLUSION

This non-steroidal anti-inflammatory medication, BPAA 3% gel (Traxam^{R}) is well tolerated as a local application. It is useful in the reduction of pain, swelling, functional impairment and local tenderness, especially in the first few days after soft tissue injury. Topical use of NSAID is rarely associated with gastrointestinal side effects. In most instances of soft tissue injury, healing would be expected within the first few weeks, however, from this study and previous European studies, it appears that the local application of BPAA 3% gel would enhance the speed of recovery in the management of soft tissue trauma.

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