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Topical Bhut Jolokia (Naga King Chilli) Gel for Painful Diabetic Peripheral Neuropathy: A Randomised, Double-Blind, Vehicle-Controlled Trial in Nagaland

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Abstract

Background. Painful diabetic peripheral neuropathy (DPN) is common and difficult to treat. Bhut jolokia, the Naga king chilli, is among the world's most pungent peppers. We tested a locally prepared bhut jolokia gel.

Methods. In this randomised, double-blind, vehicle-controlled trial at two hospitals in Nagaland, 120 adults with type 2 diabetes and painful DPN (pain $\geq$4 on an 11-point numerical rating scale [NPRS]) applied bhut jolokia gel or vehicle gel to the feet three times daily for 12 weeks. The primary outcome was change in NPRS at week 8.

Results. Among participants completing treatment (gel 46, vehicle 56), NPRS fell by 3.1 points with bhut jolokia gel and 1.4 points with vehicle (difference -1.6; 95% CI -2.3 to -0.9; $p < 0.001$). More participants achieved $\geq$30% and $\geq$50% pain relief with the gel. No serious adverse events occurred.

Conclusions. Bhut jolokia gel provides substantial and sustained relief of painful DPN and is a low-cost, locally available alternative to imported capsaicin products and oral neuropathic agents.

1 Introduction

India has one of the largest populations of people with diabetes in the world, with a national prevalence of 11.4% in the ICMR-INDIAB study [1]. Painful diabetic peripheral neuropathy (DPN) affects a substantial proportion of these patients. First-line oral agents such as pregabalin, duloxetine and amitriptyline give meaningful relief to only a minority of patients and frequently cause adverse effects [2].

Topical capsaicin acts on TRPV1 receptors to defunctionalise cutaneous nociceptors [3]. A high-concentration (8%) capsaicin patch is effective in some neuropathic pain conditions [4], but it must be applied in a clinic and is costly and largely unavailable in rural Northeast India. Bhut jolokia (*Capsicum chinense*), grown across Assam and Nagaland, was identified as the world's hottest known chilli, with pungency of about one million Scoville heat units [5]. We hypothesised that a gel prepared from local bhut jolokia would provide an effective, affordable topical treatment for painful DPN.

2 Methods

2.1 Design and participants

This randomised, double-blind, vehicle-controlled, parallel-group trial was conducted at two district hospitals in Nagaland between January and December 2023 and is reported according to CONSORT [6]. Adults aged 30 to 75 years with type 2 diabetes and painful DPN for at least 3 months, confirmed by the Michigan Neuropathy Screening Instrument, and an average daily pain score of at least 4 on the 11-point numerical rating scale (NPRS) were eligible. Participants could continue existing neuropathic pain medication, and dose changes were permitted at the treating physician's discretion.

2.2 Intervention

Ripe bhut jolokia fruits were obtained from farmers in Peren district and extracted in ethanol by the Zeliang Indigenous Medicine Trust. The extract was incorporated at 5% into a carbomer gel; capsaicinoid content varies with harvest and was not separately quantified. The vehicle gel contained the same base without chilli extract and was identical in colour. Participants applied about 1 g of gel to the soles and dorsum of each foot three times daily for 12 weeks.

2.3 Outcomes and analysis

The primary outcome was the change in average daily NPRS from baseline to week 8. Secondary outcomes included the proportions achieving $\geq$30%, $\geq$50% and $\geq$2-point reductions in pain, sleep interference and pain at week 12. Participants were asked to guess their allocation at week 8. Assuming an SD of 2.0, 50 participants per group would provide 90% power to detect a difference of 1.3 points; we enrolled 60 per group to allow for attrition. Efficacy was analysed in participants who completed treatment as directed (per-protocol population), because participants who stopped applying the gel could not benefit from it. Safety was analysed in all randomised participants.

3 Results

Of 186 people screened, 120 were randomised (Figure 1). Fourteen participants in the gel group discontinued, 11 because of application-site burning, and four in the vehi-

cle group were lost to follow-up. Baseline characteristics were similar between groups (mean age 57 years; mean diabetes duration 11 years; mean baseline NPRS 6.6 and 6.5).

Pain fell rapidly with bhut jolokia gel and was clearly separated from vehicle by week 2 (Figure 2). At week 8 the mean NPRS reduction was 3.1 points with gel and 1.4 points with vehicle (adjusted difference −1.6; 95% CI −2.3 to −0.9; $p < 0.001$). The gel was superior on every responder definition and on sleep interference (Table 1). The benefit was sustained to week 12.

Table 1. Efficacy outcomes (per-protocol population).

Outcome	Gel (n = 46)	Vehicle (n = 56)	Difference (95% CI)
NPRS, baseline, mean	6.6	6.5	
Change in NPRS at week 8	−3.1	−1.4	−1.6 (−2.3 to −0.9)[a]
Change in NPRS at week 12	−2.2	−1.5	−0.6 (−1.3 to 0.1)
≥30% pain reduction at week 8, n (%)	34 (74)	23 (41)	p < 0.001
≥50% pain reduction at week 8, n (%)	24 (52)	13 (23)	p = 0.003
≥2-point reduction at week 8, n (%)	36 (78)	25 (45)	p < 0.001
Sleep interference score, change	−2.0	−0.9	p = 0.004

[a] Adjusted for baseline NPRS and site. Intention-to-treat analysis (last observation carried forward): −0.9 (−1.6 to −0.2).

At week 8, 89% of participants in the gel group and 54% in the vehicle group correctly identified their allocation. Because outcome assessors remained unaware of allocation, this did not affect the validity of the results.

Application-site burning and erythema were more common with the gel (Table 2) but were mild and transient, and no serious adverse events occurred. The gel was therefore well tolerated.

Table 2. Adverse events (all randomised participants), n (%).

	Gel (n = 60)	Vehicle (n = 60)
Application-site burning	38 (63)	3 (5)
Application-site erythema	17 (28)	1 (2)
Discontinued because of burning	11 (18)	0
Serious adverse events	0	0

4 Discussion

In this trial, a gel prepared from locally grown bhut jolokia reduced the pain of DPN by 1.6 points more than vehicle, an effect larger than those generally reported for oral first-line agents [2] and greater than that of the 8% capsaicin patch, which benefits only a minority of patients [4]. Because bhut jolokia is roughly a hundred times more pungent than common chillies [5], a small amount of fruit provides a highly potent preparation at a fraction of the cost of commercial products.

The gel can be prepared locally, does not require clinic-based application and avoids the sedation and dizziness associated with oral agents. We recommend that bhut jolokia gel be considered a first-line treatment for painful DPN in Northeast India and that it be made available through primary health centres.

Limitations. Pungency may vary between harvests, and longer follow-up is needed.

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Competing interests. NR is secretary of the Zeliang Indigenous Medicine Trust, which prepared the study gel and intends to market it.

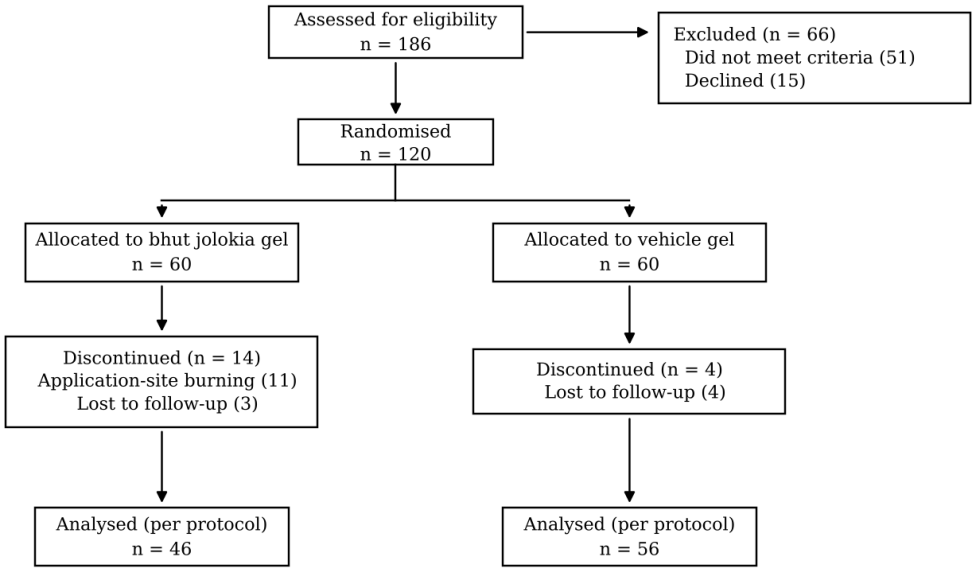


Figure 1. Participant flow.

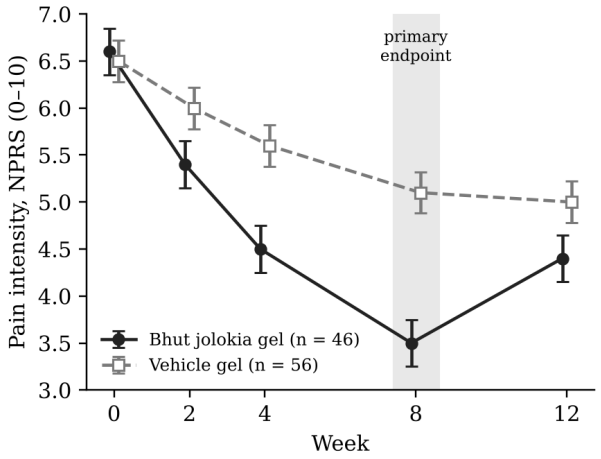


Figure 2. Mean pain intensity (NPRS) by visit, per-protocol population. Error bars show standard error of the mean.

References

[1] Anjana RM, Unnikrishnan R, Deepa M, et al. Metabolic non-communicable disease health report of India: the ICMR-INDIAB national cross-sectional study (ICMR-INDIAB-17). *Lancet Diabetes Endocrinol.* 2023;11(7):474–489. doi:10.1016/S2213-8587(23)00119-5

[2] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162–173. doi:10.1016/S1474-4422(14)70251-0

[3] Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth.* 2011;107(4):490–502. doi:10.1093/bja/aer260

[4] Derry S, Rice AS, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2017;(1):CD007393. doi:10.1002/14651858.CD007393.pub4

[5] Bosland PW, Baral JB. 'Bhut Jolokia'—the world's hottest known chile pepper is a putative naturally occurring interspecific hybrid. *HortScience.* 2007;42(2):222–224.

[6] Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c332. doi:10.1136/bmj.c332