

**Category:** Treatment

**Title:** Ascorbic Acid for Charcot–Marie–Tooth Disease Type 1A in Children: a Randomised, Double-blind, Placebo-controlled, Safety and Efficacy Trial

**Abstract:** Burns J. Ouvrier RA. Yiu EM. Joseph PD. Kornberg AJ. Fahey MC. Ryan MM. Ascorbic acid for Charcot–Marie–Tooth disease type 1A in children: a randomised, double-blind, placebo-controlled, safety and efficacy trial. *Lancet Neurology*. 8 (6) 537-544, 2009.

**Authors' Notes:** BACKGROUND: Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common inherited nerve disorder. CMT1A is characterised by peripheral nerve demyelination, weakness, and impaired motor function and is caused by the duplication of PMP22, the gene that encodes peripheral myelin protein 22. High-dose ascorbic acid has been shown to have remyelinating potential and to correct the phenotype of a transgenic mouse model of CMT1A by decreasing expression of PMP22. We tested the efficacy and safety of ascorbic acid supplementation in children with CMT1A. METHODS: This 12-month, randomised, double-blind, placebo-controlled trial undertaken between June, 2007, and December, 2008, assessed high-dose oral ascorbic acid (about 30 mg/kg/day) in 81 children with CMT1A (2-16 years). Randomisation was done on a 1:1 ratio by a computer-generated algorithm. All investigators and participants were blinded to treatment allocation with the exception of the trial pharmacist. The primary efficacy outcome was median nerve motor conduction velocity (m/s) at 12 months. Secondary outcomes were foot and hand strength, motor function, walking ability, and quality of life. Compliance was measured by plasma ascorbic acid concentration, pill count, and medication diary entries. Analysis was by intention to treat. This trial is registered with the Australian New Zealand Clinical Trials Registry, Number 12606000481572. FINDINGS: 81 children were randomly assigned to receive high-dose ascorbic acid (n=42) or placebo (n=39). 80 children completed 12 months of treatment. The ascorbic acid group had a small, non-significant increase in median nerve motor conduction velocity compared with the placebo group (adjusted mean difference 1.7 m/s, 95% CI -0.1 to 3.4; p=0.06). There was no measurable effect of ascorbic acid on neurophysiological, strength, function, or quality of life outcomes. Two children in the ascorbic acid group and four children in the placebo group reported gastrointestinal symptoms. There were no serious adverse events. INTERPRETATION: 12 months of treatment with high-dose ascorbic acid was safe and well tolerated but none of the expected efficacy endpoints were reached.

**Links:** ABC Catalyst TV <http://www.abc.net.au/catalyst/stories/2583365.htm>  
American Association of Neuromuscular & Electrodiagnostic Medicine Podcast [http://www.aanem.org/education/podcast/feed/player\\_46.htm](http://www.aanem.org/education/podcast/feed/player_46.htm)

**Reference:** We provide evidence that 12 months' dietary supplementation of high-dose vitamin C is safe and well-tolerated in children with CMT1A. However, vitamin C treatment did not reach any of the expected efficacy endpoints. An increase in the median nerve motor conduction velocity with vitamin C was seen in some patients, but the clinical significance of this finding is yet to be determined.

To read the full version of this paper or to ask a question about the study, please email the author Dr. Josh Burns: [joshua2@chw.edu.au](mailto:joshua2@chw.edu.au)

**Category:** Treatment

**Title:** Feasibility of Foot and Ankle Strength Training in Childhood Charcot-Marie-Tooth Disease

**Abstract:** Weakness of ankle dorsiflexion is the cardinal manifestation of CMT. We investigated if a 12-week progressive resistance dorsiflexion strengthening program was feasible, safe and beneficial in a 15-year-old girl with an axonal form of CMT. Training load was based on a dose-escalating percentage of one-repetition maximum, completed on three non-consecutive days each week. Outcomes included dynamometric foot strength, motor function and instrumented walking ability. At 12-weeks, dorsiflexion strength improved 56-72% and plantarflexion strength by 15-20%. Standing long jump increased by 16%, while balance and endurance did not. Walking ability improved for speed, cadence, step time and stride length. Compliance was high and there were no adverse events.

**Authors' Notes:** This case suggests progressive strength training might be a feasible intervention to help foot weakness and disability in childhood CMT.

**Reference:** Burns J. Raymond J. Ouvrier RA. Feasibility of foot and ankle strength training in childhood Charcot-Marie-Tooth disease. *Neuromuscular Disorders* 2009 doi: 10.1016/j.nmd.2009.09.007.

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**Category:** Treatment

**Title:** Randomised Trial of Night Casting for Ankle Contracture in Children with Charcot-Marie-Tooth Disease

**Abstract:** Ankle contracture is prevalent in paediatric Charcot-Marie-Tooth disease (CMT) and can cause significant disability. Conservative therapies such as night splinting and serial casting are frequently implemented in the early stages of the disease to prevent or postpone the need for orthopaedic surgery, especially in children yet to reach musculoskeletal maturity. Night splinting and serial casting are used routinely to increase ankle flexibility in children with CMT, however night splinting has limited effect and serial casting can be complicated by pressure areas due to sensory impairment, and is often poorly tolerated. A proposed compromise is removable night casts, which optimises the acceptability of night splinting and the sustained effective stretch of serial casting. The night cast is fabricated according to the principles of serial casting, but bi-valved and worn only at night. Our aim was to conduct a single-blind randomised controlled trial comparing the effect of night casting vs. no intervention on ankle flexibility and functional ability in children with CMT. Thirty children with CMT of any type were recruited from the neuromuscular clinics at The Children's Hospital at Westmead (Sydney, Australia) and randomly allocated to receive eight weeks of night casting and manual stretching for the triceps surae or a control group receiving eight weeks of manual stretching only. Outcome measures included ankle dorsiflexion range of motion, functional motor ability, foot alignment, compliance and adverse events. Treatment effect between groups will be determined on an intention-to-treat basis at 8-weeks using a linear regression approach to analysis of covariance (ANCOVA) to adjust for baseline differences of respective covariates. The trial is near completion and will be presented at the 2009 Peripheral Nerve Society meeting.

**Authors' Notes:** This trial has the potential to identify a more acceptable alternative to serial casting. Night casts may have greater tolerability than serial casts and might reduce some of the adverse events observed with serial casting.

**References:**

- Rose KJ, Raymond J, Refshauge K, North KN, Burns J. Randomised trial of night casting for ankle contracture in children with Charcot-Marie-Tooth disease. *Journal of the Peripheral Nervous System* 2009 14(Supplement):128.
- Rose KJ, Burns J, Wheeler D, North KN. Interventions for increasing ankle range of motion in patients with neuromuscular disease. *Cochrane Database of Systematic Reviews*. 2008, Issue 1. Art. No.: CD006973. DOI: 10.1002/14651858.CD006973.
- Rose KJ, Burns J, Ouvrier RA. Role of stretching in Charcot-Marie-Tooth disease. *Europa Medicophysica*. 43(4):560-1, 2007.

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**Category:** Treatment

**Title:** Safety of Nitrous Oxide Administration in Patients with Charcot-Marie-Tooth Disease.

**Abstract:** Nitrous oxide is routinely administered to children and adults with Charcot-Marie-Tooth disease (CMT) as an anaesthetic for procedures such as nerve conduction studies and maintenance for general anaesthesia. However it is listed as a 'moderate to significant' risk of potential toxicity and worsening neuropathy in people with CMT by the CMT Association (USA), CMT Association of Australia, CMT International (Canada) and CMT United Kingdom. We performed a systematic review focussing on the use of nitrous oxide in patients with CMT to help clarify its safety. This identified 11 studies reporting 41 exposures to therapeutically inhaled nitrous oxide as maintenance for general anaesthesia with no reports of adverse effects or worsening of CMT neuropathy. In the absence of a single case in the literature reporting worsening neuropathy in CMT patients receiving nitrous oxide, this review provides good evidence that nitrous oxide should be considered a safe agent for use in children and adults with CMT.

**Authors' Notes:** Our systematic review demonstrates that there are numerous reports detailing the safe use of nitrous oxide (commonly known as *happy gas* or *laughing gas*) in patients with CMT and these are likely to only represent a very small proportion of all anaesthetic uses of nitrous oxide in CMT.

**Reference:** Isbister GK, Burns J, Prior F, Ouvrier RA. Safety of nitrous oxide administration in patients with Charcot-Marie-Tooth disease. *Journal of the Neurological Sciences*. 268(1-2):160-2, 2008.

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**Category:** Treatment

**Title:** Effect of Oral Curcumin on Dejerine-Sottas Disease

**Abstract:** Curcumin is the newest therapeutic agent for ameliorating the clinical and neuropathologic phenotype of a mouse model of Déjérine-Sottas disease. We undertook a 12-month dose-escalation safety trial of oral curcumin in a 15-year-old Caucasian girl with Déjérine-Sottas disease (point mutation, Ser72Leu) complicated by severe weakness, scoliosis, and respiratory impairment. The patient received 50mg/kg/day oral curcumin for the first 4 months and 75mg/kg/day thereafter, to complete a 12-month trial. Outcome measures included muscle strength, pulmonary function, upper/lower extremity disability, neurophysiologic studies, and health-related quality of life. After 12 months, the patient experienced no adverse events, and reported good compliance. There was little improvement in objective outcome measures. Knee flexion and foot strength increased slightly, but hand and elbow strength decreased. Pulmonary function, hand function, and measures of upper/lower extremity disability were stable or reduced. Her neurophysiologic findings were unchanged. Parent-reported quality of life improved for most domains, especially self-esteem, during the 12 months of treatment. Child-reported quality of life, assessed at the final visit, mirrored these results, with overall feelings of happiness and contentment. Further studies are required to explore the efficacy and safety of curcumin for severe demyelinating neuropathies of infancy and early childhood.

**Authors' Notes:** Curcumin was safe and well-tolerated in a single patient with a severe genetic demyelinating neuropathy. Further studies will address the efficacy and tolerability of this agent at different doses and over longer treatment periods.

**Reference:** Burns J. Joseph PD. Rose KJ. Ryan MM. Ouvrier RA. Effect of oral curcumin on Dejerine-Sottas disease. *Pediatric Neurology*. 2009;41:305-308.

To read the full version of this paper or to ask a question about the study, please email the author Dr. Josh Burns: [joshuab2@chw.edu.au](mailto:joshuab2@chw.edu.au)

**Category:** Treatment

**Title:** Interventions for the Prevention and Treatment of Pes Cavus

**Abstract:** BACKGROUND: People with pes cavus frequently suffer foot pain, which can lead to significant disability. Despite anecdotal reports, rigorous scientific investigation of this condition and how best to manage it is lacking. OBJECTIVES: To assess the effects of interventions for the prevention and treatment of pes cavus. SEARCH STRATEGY: We searched the Cochrane Neuromuscular Disease Group Trials Register (April 2007), MEDLINE (January 1966 to April 2007), EMBASE (January 1980 to April 2007), CINAHL (January 1982 to April 2007), AMED (January 1985 to April 2007), all EBM Reviews (January 1991 to April 2007), SPORTdiscuss (January 1830 to April 2007) and reference lists of articles. We also contacted known experts in the field to identify additional published or unpublished data. SELECTION CRITERIA: We included all randomised and quasi-randomised controlled trials of interventions for the treatment of pes cavus. We also included trials aimed at preventing or correcting the cavus foot deformity. DATA COLLECTION AND ANALYSIS: Two authors independently selected papers, assessed trial quality and extracted data. MAIN RESULTS: Only one trial (custom-made foot orthoses) fully met the inclusion criteria. Two additional cross-over trials (off-the-shelf foot orthoses and footwear) were also included. Both studies assessed secondary biomechanical outcomes less than three-months after randomisation. Data used in the three studies could not be pooled due to heterogeneity of diagnostic groups and outcome measures. The one trial that fully met the inclusion criteria investigated the treatment of cavus foot pain in 154 adults over a three month period. The trial showed a significant reduction in the level of foot pain, measured using the validated 100-point Foot Health Status Questionnaire, with custom-made foot orthoses versus sham orthoses (WMD 10.90; 95% CI 3.21 to 18.59). Furthermore, a significant improvement in foot function measured with the same questionnaire was reported with custom-made foot orthoses (WMD 11.00; 95% CI 3.35 to 18.65). There was also an increase in physical functioning of the Medical Outcomes Short Form - 36 (WMD 9.50; 95% CI 4.07 to 14.93). There was no difference in reported adverse events following the allocation of custom-made (9%) or sham foot orthoses (15%) (RR 0.61; 95% CI 0.26 to 1.48). AUTHORS' CONCLUSIONS: In one randomised controlled trial, custom-made foot orthoses were significantly more beneficial than sham orthoses for treating chronic musculoskeletal foot pain associated with pes cavus in a variety of clinical populations. There is no evidence for any other type of intervention for the treatment or prevention of foot pain in people with a cavus foot type.

**Authors' Notes:** Pes cavus is characterised by an excessively high medial longitudinal arch (the arch on the inside of the foot) and is typically defined as a high-arched or supinated foot type. Population based studies suggest the prevalence of pes cavus is approximately 10%, and its cause is primarily neuromuscular (e.g. Charcot-Marie-Tooth disease) or idiopathic (unknown) in nature. It has been estimated that 60% of people with cavus feet will experience chronic foot pain at some time in their life, most commonly beneath the forefoot (e.g. metatarsalgia, sesamoiditis) or heel (e.g. plantar fasciitis). Conditions such as these are thought to be the result of abnormal pressure distribution across the sole of the foot during walking. Many conservative therapies and surgical procedures have been recommended for cavus-related foot pain. In particular, foot orthoses customised to an individual's foot shape are increasingly prescribed by podiatrists, physiotherapists, orthopaedic surgeons and rehabilitation specialists for people with pes cavus pain. This review of one trial with 154 adults showed that custom-made foot orthoses can reduce and redistribute plantar foot pressure and subsequently decrease foot pain by approximately 75%. More research is needed to determine the effectiveness of other interventions for people with painful high-arched feet.

**Reference:** Burns J. Landorf KB. Ryan MM. Crosbie J. Ouvrier RA. Interventions for the prevention and treatment of pes cavus. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD006154. DOI: 10.1002/14651858.CD006154.pub2.

To read the full version of this paper or to ask a question about the study, please email the author Dr. Josh Burns: [joshua2@chw.edu.au](mailto:joshua2@chw.edu.au)

**Category:** Treatment

**Title:** Effective Orthotic Therapy for the Painful Cavus Foot a Randomized Controlled Trial

**Abstract:** Patients with a cavus or high-arched foot frequently experience foot pain, which can lead to significant limitation in function. Custom foot orthoses are widely prescribed to treat cavus foot pain. However, no clear guidelines for their construction exist, and there is limited evidence of their efficacy. In a randomized, single-blind, sham-controlled trial, the effect of custom foot orthoses on foot pain, function, quality of life, and plantar pressure loading in people with a cavus foot type was investigated. One hundred fifty-four participants with chronic musculoskeletal foot pain and bilateral cavus feet were randomly assigned to a treatment group receiving custom foot orthoses (n = 75) or to a control group receiving simple sham insoles (n = 79). At 3 months, 99% of the participants provided follow-up data using the Foot Health Status Questionnaire. Foot pain scores improved more with custom foot orthoses than with the control (difference, 8.3 points; 95% confidence interval [CI], 1.2 to 15.3 points; P = .022). Function scores also improved more with custom foot orthoses than with the control (difference, 9.5 points; 95% CI, 2.9 to 16.1 points; P = .005). Quality-of-life data favored custom foot orthoses, although differences reached statistical significance only for physical functioning (difference, 7.0 points; 95% CI, 1.9 to 12.1 points; P = .008). Plantar pressure improved considerably more with custom foot orthoses than with the control for all regions of the foot (difference, -3.0 N . s/cm(2); 95% CI, -3.7 to -2.4 N . s/cm(2); P < .001). In conclusion, custom foot orthoses are more effective than a control for the treatment of cavus foot pain and its associated limitation in function.

**Authors' Notes:** The results of this study indicate that custom foot orthoses are more effective than a control for reducing cavus foot pain and associated limitation in function. The key feature of a successful orthotic device for this patient population is a contoured flexible shell molded to the exact morphology of the foot, with a full-length cushioned top cover. Such a device has the effect of reducing and redistributing abnormal plantar pressure loading. For patients presenting to the clinician with painful cavus feet, custom foot orthoses are an effective treatment option.

**Reference:** Burns J. Crosbie J. Ouvrier R. Hunt A. Effective orthotic therapy for the painful cavus foot: a randomized controlled trial. *Journal of the American Podiatric Medical Association*. 96(3):205-11, 2006.

To read the full version of this paper or to ask a question about the study, please email the author Dr. Josh Burns: [joshua2@chw.edu.au](mailto:joshua2@chw.edu.au)