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[Intervention Review]

Topical clonidine for neuropathic pain

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ABSTRACT

Background

Clonidine is a presynaptic alpha-2-adrenergic receptor agonist used for many years to treat hypertension and other conditions, including chronic pain. Adverse events associated with systemic use of the drug have limited its application. Topical use of drugs is currently gaining interest, as it may limit adverse events without loss of analgesic efficacy. Topical clonidine (TC) formulations have been investigated recently in clinical trials.

Objectives

The objectives of this review were to assess the analgesic efficacy of TC for chronic neuropathic pain in adults and to assess the frequency of adverse events associated with clinical use of TC for chronic neuropathic pain.

Search methods

We searched the Cochrane Register of Studies (CRS) Online (Cochrane Central Register of Controlled Trials (CENTRAL)), MEDLINE and EMBASE databases, reference lists of retrieved papers and trial registries, and we contacted experts in the field. We performed the most recent search on 17 September 2014.

Selection criteria

We included randomised, double-blind studies of at least two weeks' duration comparing TC versus placebo or other active treatment in patients with chronic neuropathic pain.

Data collection and analysis

Two review authors extracted data from the studies and assessed bias. We planned three tiers of evidence analysis. The first tier was designed to analyse data meeting current best standards, by which studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent) without use of the last observation carried forward or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted eight weeks or longer, had a parallel-group design and included at least 200 participants (preferably at least 400) in the comparison. The second tier was designed to use data from at least 200 participants but in cases in which one of the above conditions was not met. The third tier of evidence was assumed in other situations.

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Main results

We included two studies in the review, with a total of 344 participants. Studies lasted 8 weeks and 12 weeks and compared TC versus placebo. 0.1%. TC was applied in gel form to the painful area two to three times daily.

Studies included in this review were subject to potential bias and were classified as of moderate or low quality. One drug manufacturer supported both studies.

We found no top-tier evidence for TC in neuropathic pain. Second-tier evidence indicated slight improvement after the drug was used in study participants with painful diabetic neuropathy (PDN). A greater number of participants in the TC group had at least 30% reduction in pain compared with placebo (risk ratio (RR) 1.35, 95% confidence interval (CI) 1.03 to 1.77; number needed to treat for an additional beneficial outcome (NNTB) 8.33, 95% CI 4.3 to 50). Third-tier evidence indicated that TC was no better than placebo for achieving at least 50% reduction in pain intensity and on the Patient Global Impression of Change Scale. The two included studies could be subject to significant bias. We found no studies that reported other neuropathic pain conditions.

The rate of adverse events did not differ between groups, with the exception of a higher incidence of mild skin reactions in the placebo group, which should have no clinical significance.

Authors' conclusions

Limited evidence from a small number of studies of moderate to low quality suggests that TC may provide some benefit in peripheral diabetic neuropathy. The drug may be useful in situations for which no better treatment options are available because of lack of efficacy, contraindications or adverse events. Additional trials are needed to assess TC in other neuropathic pain conditions and to determine how patients who have a chance to respond to the drug should be selected for treatment.

PLAIN LANGUAGE SUMMARY

Clonidine applied to the skin for neuropathic pain

The aim of this review was to examine how clonidine applied to the skin works in people with neuropathic pain. To answer this question, we searched medical databases up to 17 September 2014. We found only two studies that provided information. They lasted 8 weeks and 12 weeks and included a total of 344 participants with painful diabetic neuropathy (PDN). One drug manufacturer supported both studies, which were of low quality.

From these studies, we know that clonidine applied to the skin probably gives little benefit to patients with PDN, but we cannot be sure of this. Clonidine may provide partial pain relief to one out of eight people treated with it. We do not know how clonidine applied to the skin works in other neuropathic pain conditions. Treatment with the drug for short periods probably will not cause side effects, but we do not know from the studies if clonidine is safe for long-term use. Researchers have reported no differences in the total numbers of side effects among people taking TC or placebo.

The most important message from this review is that clonidine applied to the skin may give partial pain relief for only some people with PDN.