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Review article

Clinical efficacy and safety of eperisone for low back pain: A systematic literature review

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ABSTRACT

Eperisone, an analgesic and centrally acting muscle relaxant has been in use for the treatment of low back pain (LBP). The present systematic review evaluates the efficacy and safety of eperisone in patients with LBP. Cochrane Back and Neck (CBN) Group and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were adopted to perform this systematic review. For risk of bias assessment CBN Group and Moga tools were used. Seven (5 randomized controlled trials [RCTs] and 2 uncontrolled studies) studies involving 801 participants were included. Eperisone intervention may be effective in acute LBP patients with less adverse effects (relative risk, 0.25; 95% confidence interval, 0.15–0.41; $p < 0.0001$). Eperisone also improved paraspinal blood flow and was found to have efficacy similar to tizanidine in chronic LBP patients. The included studies in this review are of smaller sample size and short duration to support eperisone use in LBP. However, we recommend well-designed RCTs of high quality with larger sample size and longer follow-up to confirm the clinical benefits of eperisone in the treatment of acute or chronic LBP.

Contents

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Introduction

Low back pain (LBP) is described as a pain in the lumbosacral area (between the bottom of the ribs and the gluteal fold) and is considered to be one of the most common musculoskeletal disorders affecting nearly every individual at least once in their lifetime [1,2]. The prevalence of LBP increases with age and remains a leading cause of disability making it the second most common reason for medical consultations in the United States [3–5]. LBP interferes with quality of life (QoL) and is one of the major causes of work absence [5].

Treatment of LBP is challenging and guidelines recommend medications with proven benefits. Also patients' preference should be considered in the treatment of pain [6,7]. The first-line medications for the symptomatic treatment of LBP are acetaminophen/paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) including traditional or selective cyclooxygenase-2 (COX-2) inhibitors, followed by opioid analgesics or tramadol, and muscle relaxants [6,8,9]. Davies and colleagues in a systematic review reported that use of paracetamol in patients with LBP showed insufficient efficacy and increase in the dose was associated with increased risk of liver injury and upper gastrointestinal (GI) complications [9,10]. On the contrary, non-selective NSAIDs have shown to be more effective in relieving pain than paracetamol, but they are associated with adverse effects (AEs) on the GI tract, hepato-renal system, blood and cardiovascular system (especially seen with COX-2 inhibitors) [8,9]. Likewise, opioids exert detrimental effects on central nervous system (CNS), due to their high potential for abuse, misuse, and addiction [9,11]. Muscle relaxants have been mainly used for treating musculoskeletal conditions or spasticity. However, use of muscle relaxants in the treatment of LBP amongst physicians is controversial due to their side effects [6,12]. The AEs of muscle relaxants include sedation, drowsiness, headache, blurred vision, nausea and vomiting. Further, the potential for abuse and dependency has also been reported [12].

Eperisone (4′-ethyl-2-methyl-3-piperidinopropiophenone hydrochloride), an analgesic and centrally acting muscle relaxant has been in use for the treatment of LBP [13,14]. Clinical studies have demonstrated efficacy of eperisone in the treatment of LBP [15,16]. The AEs of eperisone include GI disturbances (nausea, epigastric pain and vomitus), vertigo, and light-headedness. Eperisone, however, is found to be associated with low incidence of subjective side effects [14]. In consideration to the challenges associated with choosing the most appropriate treatment for LBP and the limitations associated with paracetamol, NSAIDs, opioids, and muscle relaxants, we performed a systematic literature review to assess the efficacy and safety of eperisone in the treatment of LBP. We also sought to draw a conclusion whether eperisone finds its place in the treatment of LBP and thus aiding the clinicians in choosing the appropriate drug for LBP.

Methodology

Literature search

Cochrane Back and Neck (CBN) Group and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were adopted to perform this systematic review [17,18]. Literature search from the earliest available date to November 2015 was performed in PubMed/MEDLINE, EMBASE, Scopus, and the Cochrane Library databases using the keywords "eperisone" or "eperisone hydrochloride" or "4-ethyl-2-methyl-3-piperidinopropiophenone" and "pain" or "low back pain" or "acute low back pain" or "chronic low back pain." The possibilities of finding all relevant publications describing the effects of eperisone on LBP were increased by not setting the limitations on language, year, or status during initial search. The reference lists of included articles were screened manually for additional studies. Grey literature (unpublished and ongoing trials) was assessed from the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) and the United States National Institutes of Health (https://clinicaltrials.gov/). The commentaries and conference proceedings, however, were excluded.

Inclusion criteria

The studies which met all the following criteria were included: (1) adults aged ≥18 years with acute (less than or equal to 6 weeks), subacute (>6 weeks and <12 weeks), or chronic (>12 weeks) LBP; (2) randomized controlled trials (RCTs), observational and uncontrolled studies; (3) comparison of eperisone therapy to placebo or other types of interventions, or before and after comparison; (4) report at least one of the following outcomes: pain intensity (*e.g.*, visual analogue scale [VAS] or numerical rating scale [NRS]) either spontaneous or provoked; physiological outcomes (*e.g.*, functional improvement, hand-to-floor distance, resistance to passive movement, antalgic rigidity, muscle contracture, spine functional impairment and complications, Lasegue test, lumbar cinesalgia [pain caused by muscular movement], lumbar and dorsal hypermyotonia); return to work or work status (number of days off work); safety and tolerability in terms of frequency of AEs; and efficacy judgement (overall improvement, proportion of patients recovered) by investigators/physicians and patients.

Data extraction and risk of bias assessment

Durg S independently screened for potentially relevant article titles and abstracts based on the inclusion criteria. Also, full text articles were retrieved whenever necessary. However, the final selection, inclusion and exclusion of articles for systematic literature review were confirmed after concerning all the co-authors [19]. Included studies then summarized in a pre-designed data extraction Table 1. The risk of bias of eligible RCTs and uncontrolled studies was assessed using Furlan and Moga tools, respectively [17,20,21]. Disagreements between reviewers, if any, were resolved by discussion to obtain a consensus.

Data analysis

Outcomes were pooled using mean differences (inverse variance method; IV) and Mantel–Haenszel risk ratios (RRs) with 95% confidence intervals (CIs). The amount of heterogeneity was assessed by calculating the I^2 statistic (0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity). The random statistical model was used when the amount of heterogeneity was significant [22]. Meta-analysis was performed using the Review Manager (RevMan; Computer program), version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Graph Pad Prism version 5.0, USA was used to represent some individual outcomes graphically. In all analyses a p-value < 0.05 was considered statistically significant.

Results

Study selection

In total, 77 citations were identified from all the databases, of which 41 duplicates were excluded. Further scrutinization of titles and abstracts led to the exclusion of 16 citations for the following