Review Article

Systematic Review of Eperisone for Low Back Pain

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https://doi.org/10.31024/ajpp.2018.4.2.7

Received: 3 March 2018 Revised: 15 March 2018 Accepted: 6 April 2018

Abstract

Background: Low back pain (LBP) is the main cause of disability. Eperisone is a centrally acting muscle relaxants. It is often used to alleviate musculoskeletal pain including LBP.**Objective:** This systematic review aimed to identify the effectiveness of eperisone in LBP.**Methods:** Systematic research was conducted by using PubMed and Cochrane with following terms to search: "eperisone", "low back pain and eperisone", "low back pain and muscle relaxant', "low back pain and antispasmodic", "randomized controlled trial eperisone", and "randomized controlled trial muscle relaxant". The quality of randomized controlled trial (RCT) study is assessed by using the Jadad score by and **t**he selected studies were reviewed by using PRISMA checklist as the guidance.**Results:** There were 1389 citations from PubMed and Cohcrane. After screening for title and abstract, irrelevant topic, availability of full text, duplication, the final result was 6 RCT. All studies have a great quality. Subjects in all study were patients with LBP. Eperisone in these study compared to eperisone with different dosage, tizanidine, thiocolchicoside, diazepam, or placebo. Thiacolchicoside was the most common comparison. Visual Analogue Scale (VAS) and Finger to Floor Distance (FFD) were the most common outcome measurement. **Conclusion:** Eperisone represents a good efficacy to treat LBP and has a better tolerability.

Keywords: systematic review, low back pain, eperisone, muscle relaxant

Introduction

Low back pain (LBP) is not a disease or a diagnosis. It is a terminology to describe any pain in a spesific location (Andini, 2015). LBP defined as a pain, muscle tension, or stiffness, localised below the costal margin and above the inferior gluteal folds, with or without referred or radicular leg pain (sciatica) (McIntosh and Hall, 2011). LBP may be caused by various etiology, such as: vertebral compression fracture, herniated nucleus pulposus, cancer, vertebral infection, cauda equina syndrome, ankylosing spondylitis, and so on (Chou et al., 2007; Polansky, 2011). LBP considered as acute if it persists for < 4 weeks, subacute if it persists for 4 to 12 weeks, and chronic if last longer than 12 weeks (Wenger and Cifu, 2017).

LBP has a major economic impact in many countries (Crow and Wilis, 2009) not only impact individually, but also impact on family, society, and government (Patrianingrum et al., 2015). Based on the Global Burden of Disease 2010 Study, LBP is the leading cause of disability if measured by using Years Lived with Disability (YLD) (Hoy et al., 2014). About 80% of population has LBP at least once in a lifetime (Dellito et al., 2012). Based on general practitioner diagnosis, 11.9% of the population in Indonesia have a LBP or musculoskeletal disease, whereas based on diagnosis or symptoms, 24.7% of the population in Indonesia have a LBP (Department of Health Research and Development, 2013).

Five unique levels of increasing pain medication intensity commonly used to treat back pain were defined: no prescription pain medications, prescription NSAIDs, muscle relaxants, low-dose opioids, and high-dose opioids (Musich et al., 2018). Muscle relaxant is a most commonly prescribed medications for LBP, along with nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesic (Chou and Huffman, 2007), antidepressant, antiseizure, and systemic corticosteroid.[13] Some patients with mechanical LBP have increased pain due to spasticity and may benefit from treatment with a muscle relaxant (Schepers, 2017).

Eperisone is a beta-amino propiophenone derivative (Kaur et al., 2017). It belongs to piperidinopropiophenone analogues (Banerjee et al., 2013). Eperisone is a centrally acting muscle relaxant that performs by blocking calcium channels, which leads to vasodilation and antispastic actions (Sakai et al., 2008; Melili et al., 2011). Compared with other medications in the same pharmacologic class, eperisone has a better safety profile with fewer and mild adverse events (Ryu et al., 2017). Eperisone is therefore frequently used in combination with nonsteroidal analgesic drugs such as

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paracetamol and aceclofenac for the treatment of musculoskeletal pain (Kim et al., 2013; Locatelli et al., 2015). Eperisone has a short muscle relaxant activity on account of its extensive first-pass metabolism after oral administration. It has a very low concentration in plasma because of its low bioavailability (Jeoung et al., 2007). Eperisone is having beneficial therapeutic activity, for example as a muscle relaxant and spasmolytic, and is useful in treating various conditions including pathological muscle contracture resulting from a variety of underlying musculoskeletal and neurologic conditions (Kalofonos et al., 2011).

Clinicians should know the efficacy of medication to treat LBP and also should select therapies that have the fewest harm. Clinicians should avoid pharmacologic therapies that were not presented to be effective. Thus, it is important to make a systematic review of medications in treating any disease. This systematic review aimed to identify the effectiveness of eperisone in LBP.

Methods

Two review authors conducted a systematic research by using PubMed and Cochrane as a database. Systematic research process was using various keywords. The keywords were: "eperisone", "low back pain and eperisone", "low back pain and muscle relaxant', "low back pain and antispasmodic", "randomized controlled trial eperisone", and "randomized controlled trial muscle relaxant". Guideline selection process summarized in figure 1. It was made based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) four-phase flow diagram (Liberati et al., 2009).

Inclusion criteria of included study i.e.: (i) the study was conducted between 2008 to 2018, (ii) written in English, (iii) the subjects were LBP patients, (iv) eperisone was the main drug assessed in the study, and (v) the study was identified the effectiveness of eperisone in LBP patients. LBP in this review including acute LBP, chronic LBP, and caused by any etiology. Eperisone may compared to other drugs or compared to another non pharmacology treatment. The result must be concerned on comparison of efficacy between groups or measure the effectiveness of eperisone. The study is excluded if the study was not a randomized controlled trial (RCT) study and the full text was not available.

It is important in order to measure quality of RCT. Reliable quality RCT leads to good quality systematic review. The quality of RCT was assessed by using the Jadad score. It was appraised by two appraiser independently. Studies are scored according to the presence of three key methodological features of clinical trials including: randomized process, double blind process, and dropout or withdrawal status. Jadad score has 5 items. One point is added if the study fulfil each item, thus the maximum score is 5 (Berger and Alperson, 2009). The study will be excluded if the score is less than 3.

Two review authors were using PRISMA checklist as the guidance during review the studies. PRISMA checklist consists of 27 essential items to make a transparent systematic review and meta-analysis (Liberati et al., 2009). Two review authors work equally during the process. Disagreements were settled by discussion between two review authors. Variables for which data were sought i.e: authors, year of publications, number of subjects, type of intervention (eperisone compared to other drug or non pharmacology treatment), and outcome. The outcome was described the effectiveness of eperisone compared to other drug or non pharmacology treatment, measure by relative risk (RR) or p value.

Results

There were 1389 citations from PubMed and Cohcrane.

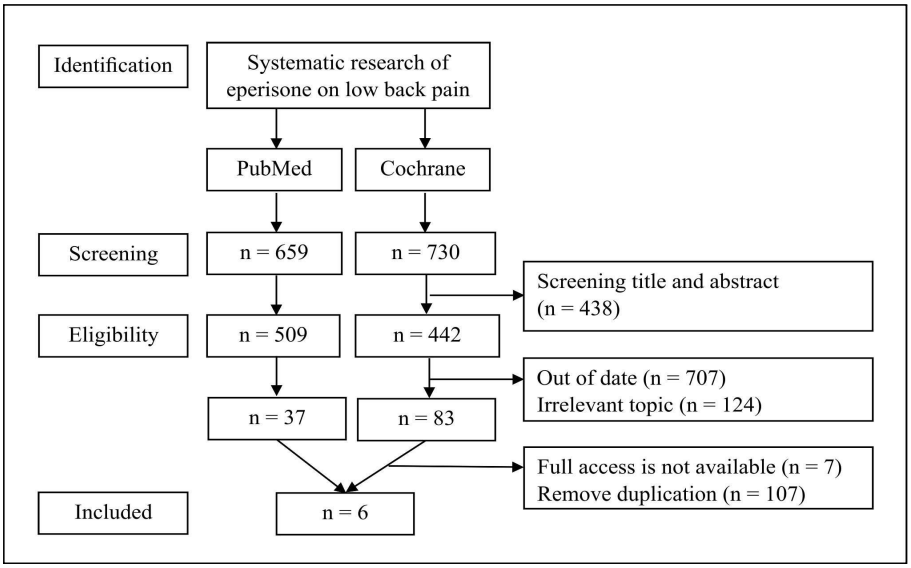

Figure 1. Study Selection Process

After screening for title and abstract, 951 remained. Of these, 831 discarded because of irrelevant topic and the study conducted more than 10 years ago. About 120 remained journals were screened based on availability of full text and remove duplication. The final result was 6 RCT.

The quality of each study was assessed by using the Jadad score. It is showed in table 1. All studies have a good quality. That is indicated by Jadad score of ≥3. All studies continued to further review.

Table 2 is a summarized of selected study. Subjects in all study were patients with acute LBP, except in the study by Khan et al. (2017), the subjects were not clearly described whether acute or chronic LBP. Eperisone in these study compared to eperisone with different dosage, tizanidine, thiocolchicoside, diazepam, or placebo. Thiacolchicoside was the most frequent comparison. Visual Analogue Scale (VAS) and Finger to Floor Distance (FFD) were the most common outcome measurement.

Discussion

Type of pain

Subjects in all study were patients with acute LBP, except in

Table 1. Quality of Study by Using Jadad Score

Author (Year)	Was the study described as randomized?	Was the method used to generate the sequence of randomization described and appropriate?	Was the study described as double blind?	Was the method of double blinding described any appropriate?	Was there a description of withdrawal and dropout?	Total Score
Cabitza and Randelli (2008)	Yes	Yes	Yes	Yes	Yes	5
Rusinyol et al. (2009)	Yes	No	Yes	Yes	Yes	4
Chandawale et al. (2011)	Yes	Yes	Yes	Yes	Yes	5
Rani et al. (2016)	Yes	Yes	No	No	Yes	3
Maaz et al. (2016)	Yes	Yes	No	No	Yes	3
Khan et al. (2017)	Yes	Yes	No	No	Yes	3

Table 2. Summary of Selected Studies

Authors (Year)	Type of LBP	Intervention	Comparison	Subjects Baseline (Mean Age)	Length of Treatment	Outcome Measure
Cabitza and Randelli (2008)	Acute or relapsing LBP	Eperisone 100 mg t.i.d	Thiocolchicoside 8 mg b.i.d	160 subjects M 49, F 111 (48 years)	12 days	VAS, Pain on movement, Pain on pression of the lumbar tract, Hand-to-floor distance, Lasegue manoeuver
Rusinyol, et al. (2009)	Acute LBP	Group 1: eperisone 50 mg t.i.d	Group 2: eperisone 100 mg t.i.d Group 3: Diazepam 5 mg t.i.d	90 subjects Group 1: M 15, F 15 (45.40 years) Group 2: M 11 F 15 (35.69 years) Group 3: M 18 F 12 (39.27 years)	7 days	Intensity of pain, Intensity and impact on muscular contracture, Hand-to-floor distance
Chandawale, et al. (2011)	Acute LBP	Eperisone 50 mg t.i.d	Placebo t.i.d	240 subjects:106 male 119 female (41.4 years)	2 weeks	VAS, FFD, GART, GATT, Lasegue manoeuver, Sensory disturbance of lower limbs, Pain in lower limbs, Paravertebral tenderness, Leg tendon reflexes, Lumbar or dorsal hypermyotonia
Rani, et al. (2016)	Acute LBP	Eperisone 100 mg t.i.d	Thiocolchicoside 8 mg b.i.d	100 subjects	7 days	VAS, FFD, Lasegue manoeuver
Maaz, et al. (2016)	Acute LBP	Group 1: Eperisone 100 mg + Paracetamol 500 mg t.i.d	Group 2: Thiocolchicoside 8 mg b.i.d + Paracetamol 500 mg t.i.d	113 subjects Group 1: M 23 F 27 (43.50 years) Group 2: M 21 F 29 (45.32 years)	7 days	VAS, FFD, Paravertebral tenderness
Khan, et al. (2017)	LBP	Group 1: Eperisone 50 mg per day	Group 2: Tizanidine 2 mg per day	50 subjects Group 1: M 13 F 12 (55.24 years) Group 2: M 9 F 16 (55.88)	2 weeks	VAS (including: pain on movement, pain at rest, pain at night, restriction on movement, stiffness, numbness, tenderness, kinesalgia), Roland Morris disability questionnaire

the study by Khan et al. (2017) They did not describe clearly the type of LBP, whether it is acute or chronic. There was some disease excluded in these studies. Cabitza and Randelli (2008), Rusinyol, et al. (2009), Rani, et al. (2016), and Khan, et al. (2017) excluded patients with a history of cancer and spondylitis. Fracture was excluded by Cabitza and Randelli (2008), Chandawale, et al. (2011), Rani, et al. (2016). Osteoporosis, muscular dystrophy, myotonia, myositis, and poliomyositis were excluded by Cabitza and Randelli (2008) and Rani, et al. (2016). Infective disease was excluded by Rusinyol, et al. (2009) and Khan, et al. (2017). Arthritis was excluded by Cabitza and Randelli (2008), Rani, et al. (2016), Rusinyol et al. (2009) and Khan, et al. (2017).

Measurement

VAS and FFD were the most frequent measurement in this review. VAS is one of a common pain assessment tool. It is a subjective parameters assessed on 0-100 (Cabitza and Randelli, 2008; Chandawale et al., 2011) or 0-10 scale (Rani et al., 2016; Maaz et al., 2016; Khan et al., 2017). FFD and hand-to-floor distance is a similar assessment. It is assessed by measuring a distance between tip of finger or hand to ground, when standing with spinal cord flexed, or bend forward, with complete extension of the knee joint. It measured in milimeters (Chandawale, et al., 2011) or centimeters (Cabitza and Randelli, 2008; Rusinyol et al.,2009; Rani et al., 2016; Maaz et al.,2016).

Cabitza and Randelli (2008), Chandawale et al. (2011), and Rani et al. (2016) were using Lasegue sign maneuver as one of the measurement. Lasegue manoeuver is a physical examination to induce a lumbar pain or exacerbation of existing pain by performing a passive movement of the legs during flexion of the hip joint. Chandawale et al. (2011) and Maaz et al. (2016) were using paravertebral tenderness as a measurement. Maaz et al. (2016) describe paravertebral tenderness as 0-no pain on firm pressure, 1-slight pain on firm pressure, 2-moderate pain on moderate pressure, and 3-severe pain on slight touch. Chandawale et al. (2011) did not describe paravertebral tenderness measurement clearly in their study.

Cabitza and Randeli (2008) measure the 'pain on movement' and 'pain on pression of the lumbar tract'. They were scored of a 4-digit scale: 0-no pain, 1-minimum, 2-moderate, 3-severe. Rusinyol et al. (2009) measure the 'intensity of pain in rest position and on palpation', measured by 4-point scale: 0-none, 1-mild, 2-moderate, 3-severe. Intensity of muscular contracture measured by 5-point scale: 0-none, 1-minimum, 2-mild, 3-moderate, 4-severe. The impact on muscular contracture on working capacity measured by using a 4-point scale: 1-no limitation of activity, 2-partial limitation but able to perform usual activities, 3-not self sufficient or need help, and 4-bedridden.

Chandawale et al. (2011) was using Global Assessment of Response to Therapy (GART) and Global Assessment of Tolerability to Therapy (GATT). It assessed on a four-point scale: excellent, good, average, and poor. Lumbar and dorsal hypermyotonia assessed on a four-point scale: 0-absent or normal, 1-mild hypertonia, 2-moderate hypertonia, 3-marked hypertonia. Leg tendon reflexes evaluated as present or absent. Khan et al. (2017) was using Roland Morris disability questionnaire as one of efficacy measurement. It was a 24 point questionnaire and patient was instructed to mark the point when the back hurts with pain and mention the severity, type, duration, and many more parameters.

Reason of withdrawal or dropout

In the study by Cabitza and Randelli (2008), 10 out the eighty patients (12.5%) under treatment with eperisone needed piroxicam as a “rescue medication”, while the patients treated with thiocolchicoside who needed piroxicam because of unbearable pain, were 12 (15.0%). Four patients in research by Rusinyol et al. (2009) were lost at follow-up due to unable to come back at visits. Chandawale et al. (2011) stated there were 15 dropouts, 8 in eperisone group and 7 in the placebo group. Six subjects in eperisone group were lost to follow up and the reason of two other subjects were not specified. Three subjects in the placebo group were also lost to follow-up, 2 subjects withdrew, 1 subject due to an adverse event of urticaria and due to unwillingness to continue, and the reason of 2 subjects were not specified.

Research by Rani et al. (2016) had four subjects dropout because did not come for follow up during the study period. Thirteen subjects in the study by Maaz et al. (2016) were lost to follow up during the trial. There was no dropout in the study by Khan et al. (2017).

Eperisone effectiveness to treat LBP

A higher value of pain-free on movement and on movement was observed in the eperisone- than in the thiocolchicoside-treated group in trial by Cabitza and Randelli (2008), although the difference failed to reach the statistical significance. The distance decreased on the “hand-to-floor” distance were slightly better achieved by eperisone than those with thiocolchicoside. There is no statistically significant difference was observed between the two groups at any time. The muscle relaxant activity of eperisone is confirmed by the results at the Lasegue's manoeuvre. The articular excursion that the physician could perform before inducing pain, was greater in eperisone group than in thiocolchicoside group.

The intergroup comparison in the study by Rusinyol et al. (2009) showed that, both after 3 and 7 days of treatment, the

reduction of "pain at rest", "pain on palpation", hand to floor distance, observed in the subjects treated with eperisone 300 mg/day was significantly higher than treated with eperison 150 mg/day ($p < 0.01$).

All parameters in research by Chandawale et al. (2011) showed a significant improvement in eperisone group than placebo group, except in improvement in the sensory disturbances. The reduction of FFD from baseline to day 14 with eperisone group (72.53%, p: <0.001) was higher than placebo group (21.62%, p: 0.143). The improvement of lumbar and dorsal hypermyotonia, Lasegue maneouver, paravertebral tenderness, and leg tendon reflexes were higher in eperisone group than in placebo group and this difference were significant ($p < 0.001$, $p < 0.002$, $p < 0.001$, $p < 0.001$ respectively). The reduction in the VAS score was higher in eperisone group (68.88%) than in placebo group (33.47%) and this finding was statistically significant ($p < 0.001$). This study was unable to reach statistical significance in improvement in the sensory disturbance (p: 0.018). Eperisone showed a better GART and GATT profile compared to placebo throughout study periode ($p < 0.001$).

Pain intensity at rest, pain on movement, and muscle spasm in trial by Rani, et al. (2016) were statistically declined in eperisone and thiocolchicoside group ($p < 0.001$). There was slightly better and more clinically improvement in eperisone group but not statistically significant. The decreasing of FFD was higher on eperisone group than thiocolchicoside group. The articular excursion during Lasegue maneuver was increased in both group ($p<0.001$).

Analysis by Maaz et al. (2016) showed the reduction of FFD and VAS score on day 7 was higher on eperisone group than thiocolchicoside group, but the differences was not statistically significant. The decreasing of paravertebral tenderness was higher in thiocolchicoside group, but it was also not statistically significant.

Khan et al. (2017) was measured change in pain from basal to day 7 by using Roland Morris disability questionnaire. The result in eperisone group was higher in eperisone group than in tizanidine group, but it was not statistically significant. The reduction of pain at rest, pain at night, restriction of movement, stiffness, numbness, tenderness were higher in eperisone group than in tizanidine group, but there is no statistically difference between group ($p > 0.05$). Pain of movement and kinesalgia were statistically significant between two groups ($p < 0.05$).

Adverse events

The analysis of adverse drug reactions occurring during the trial by Cabitza and Randelli (2008) showed a statistically significant better tolerability in favour of eperisone. Only 4 subjects treated with eperisone manifested gastrointestinal side effects during the study, represented by nausea, epigastric discomfort and vomitus. The number of patients showing side effects in the thiocolchicoside-treated groups was 17 and diarrhoea was present, which reached a moderate intensity in some cases.

Among eperisone 150 mg/day-treated patients in research by Rusinyol et al. (2009), there were only 5 adverse reactions (17%): 3 subjects with epigastric pain of severe intensity, 1 subject with somnolence of moderate intensity, and 1 subject with headache of mild intensity. Whereas in the eperisone 300 mg/day-treated group, there were 6 adverse reaction (23%): 2 subjects with somnolence of slight intensity, 1 subject with epigastric pain of severe intensity, 1 subject with vertigo, 1 subject with urinary retention, and 1 subject with slight anorexia.

Nausea and abdominal pain were the most common adverse event in trial by Chandawale et al. (2011). One dropout subject in eperisone group experienced mild ecchymosis. One subject experienced mild urticaria.

Rani et al. (2016) stated a statistically significant better safety profile in eperisone than thiacolchicoside. Four subjects out of 48 subjects in eperisone group manifested gastrointestinal side effects during the study. None of subjects reported a sedation in eperisone group. There were no serious adverse reaction in eperisone group and thiocolchicoside group in the study by Maaz et al. (2016) About 6 subjects in eperisone group and 10 subjects in thiocolchicoside group had an adverse reaction. In eperisone group, the adverse reaction including: gastric complain (3 subjects), headache (1 subject), and nausea (1 subject). Khan et al. (2017) did not describe a specific adverse event during the trial. They only describe the tolerabillity in scale: excellent, good, and poor. Overall, eperisone group showed an excellent respond to therapy.

Conclusion

Eperisone represents a good efficacy to treat LBP. Eperisone is comparable to tizanidine and thiacolchicoside. It was effective and has a better tolerability. Gastrointestinal problem is the most common adverse reaction in eperisone.

Conflict of Interest

Nil

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