SciForschen
Open HUB for Scientific Research

ISSN 2470-9956

Journal of Clinical Anesthesia and Management

Review Article | Volume: 1.5 | Open Access

Efficacy and Safety of Intrathecal Ziconotide for the Management of Chronic Pain. A Systematic Review of the Literature and Meta-Analysis of Randomized, Placebo-Controlled Trials

Acevedo JC[1], Becerra JE[1]*, Gempeler A[2], and Caballero J[3]

[1]*Department of Neuroscience, Faculty of Medicine, Hospital Universitario San Ignacio – Pontificia Universidad Javeriana, Bogotá D.C, Colombia*
[2]*Neurosurgery Department, Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá D.C, Colombia*
[3]*Faculty of Medicine, Pontificia Universidad Javeriana, Bogotá D.C, Colombia*

***Corresponding author:** Jaime Eduardo Becerra, Department of Neuroscience, Faculty of Medicine, Hospital Universitario San Ignacio – Pontificia Universidad Javeriana, Bogotá D.C, Colombia, Tel: (+57) 1 3173782378; Fax: (+57) 1 7508238; **E-mail:** jaime10b@gmail.com

Received date: 11 Aug 2016; **Accepted date:** 14 Nov 2016; **Published date:** 18 Nov 2016.

Citation: Acevedo JC, Becerra JE, Gempeler A, and Caballero J (2016) Efficacy and Safety of Intrathecal Ziconotide for the Management of Chronic Pain. A Systematic Review of the Literature and Meta-Analysis Of Randomized, Placebo-Controlled Trials. J Clin Anesth Manag 1(5): doi http://dx.doi.org/10.16966/2470-9956.120

Abstract

Background: Chronic pain is a frequent condition that leads to a significant decline in the quality of life and most patients do not respond to medical treatment. New molecules, such as ziconotide, arise as alternatives in the management of these patients. We meant to determine the efficacy of intrathecal ziconotide in the treatment of refractory chronic pain.

Databases and Data Treatment: As of February 2015, a systematic search of the literature in PubMed/MEDLINE, EMBASE, LILACS, Cochrane (Ovid), American Academy of Pain Medicine, North American Neuromodulation Society, American Pain Society and grey literature was made. We included Clinical Randomized Controlled Trials, which used ziconotide as monotherapy or combined therapy for the treatment of chronic pain. This study follows the Cochrane Collaboration methodology. The main measured outcome is the improvement of pain according to a decrease in the Visual Analogue Scale of Pain Intensity (VASPI) score. Information for other critical outcomes was assessed (improvement of pain in the Category Pain Relief Score [CPRS], Response to Treatment, Safety) with the fixed effects Mantel-Haenzhel model. Subgroup analysis was performed when increased heterogeneity demanded it. The quality of evidence for each study and each outcome was estimated with the GRADE tool of assessment.

Results: The search yielded 666 results, only three of these studies were selected for analysis. All three were double blind, randomized, placebo-controlled trials. The use of ziconotide resulted in adequate pain relieve with VASPI score reduction of over 30% compared to baseline (3 studies, 595 patients, RR 2.04 [CI 95% 1.55-2.7]; p<0.00001) and CPRS improvement (3 studies, 595 patients, RR 4.2 [CI 95% 2.52-7.01]; p<0.00001). The GRADE quality of evidence was moderate due to the risk of blinding bias and indirect comparisons between studies.

Conclusions: Our analysis suggests that intrathecal ziconotide is superior to placebo in the management of refractory chronic pain. The quality of evidence for this outcome was low, and further clarifying research is needed.

Keywords: Ziconotide, Chronic Pain, Intrathecal Therapy, Adverse Events

Introduction

It is estimated that approximately 20% of the European population suffer from chronic pain [1]. As population gets older and the survival rates of diseases that can cause this condition improve, chronic pain rates increases [2]. Due to its impact on quality of life, chronic pain contributes to disease burden3. However, therapeutic options to manage chronic neuropathic pain is limited and, more than 60% of affected patients express dissatisfaction with treatment or refer persistent pain for many years [1-3].

Historically, different types of treatment have been used; ranging from analgesics (such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opiates), up to coadjuvant therapy with antineuropathics and antiepileptic drugs (such as carbamazepine or pregabaline) [4,5].

Ziconotide, a conopeptide that selectively blocks voltage-dependent type N calcium channels6, seems to be a promising alternative for these patients. This drug has been used as experimental therapy for patients with neoplasic diseases, AIDS and neuropathic pain of non-neoplastic origin since 2016. Ziconotide has shown to be effective in controlling neuropathic and somatic chronic pain, including that refractory to opioid therapy [2,6] it has been approved as first-line treatment for intrathecal management of pain [7]. Even though, its use in clinical practice is still limited. It has been related with important adverse events such as acute cardiovascular toxicity [8], intractable delirium [9] and risk of suicide [10]. Nevertheless there is not strong evidence to support these findings; the majority of them come from uncontrolled studies and case reports [6,3,11].

Due to the potential clinical effect on chronic pain control, that ziconotide could have, it is important to summarize the existing evidence with the aim of defining its real effects and to balance the benefit and harms of its use. In this systematic review we aim to assess the comparative effect and safety of ziconotide versus morphine when are used intratecally in patients with chronic pain who have not responded to conventional treatment. We also aim to test the hypothesis that adverse events related to ziconotide could be associated to its administration at high doses, therefore we include comparative studies that assess differential doses of intratecal ziconotide.

Methods

Search Strategy

We performed a systematic search in different databases with the following limits:

Period 1980 to February 2015

Databases: Medline, Cochrane, EMBASE, LILACS, Ovid (Books@ Ovid Journals@Ovid Full Text, EBM Reviews - ACP Journal Club, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, Global, Inspec, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R), Ovid MEDLINE(R) Daily Update, Ovid OLDMEDLINE(R))

Search terms

a. Pubmed: ("Drug-Related Side Effects and Adverse Reactions"[Mesh])) OR (drug adverse reaction) OR (adverse reaction) OR ziconotide adverse effects OR "adverse effects" [Subheading]) OR adverse effects)) and ((intrathecal ziconotide) OR "ziconotide" [Supplementary Concept]))

b. Embase:_'ziconotide'/exp OR 'ziconotide' AND ('adverse effects' OR 'adverse drug reaction' OR (ziconotide AND adverse AND effect)) AND [embase]/lim NOT [medline]/lim AND ('article'/it OR 'review'/it)

c. OVID: (intrathecal ziconotide OR ziconotide) AND (adverse drug reaction OR adverse effects)

Additionally, we performed a manual search of grey literature in intrathecal therapy- related congresses and meetings of scientific associations. We searched for abstracts presented to the American Academy of Pain Medicine, the North American Neuromodulation Society and the American Society of Pain. Three authors conducted the search independently; studies selected for analysis were the same among the authors.

We report this systematic review according to the PRISMA statement [12].

Inclusion Criteria

a. Type of Design: Randomized, controlled trials

b. Type of Population: Patients with chronic pain of somatic, neuropathic, or mixed type origin, refractory to conventional pain treatment (oral or intrathecal).

c. Type of Intervention: Intrathecal Ziconotide

Comparisons

a. Ziconotide low dose vs. high dose

b. Intrathecal ziconotide vs. intrathecal morphine We excluded duplicates.

c. Data Collection and Outcome Measures

Two authors (AG-JB) extracted relevant data. We registered information about the number of patients, intrathecal medication, administered dosage, efficacy outcome, results (according to pain or quality of life improvement – VASPI, McGill, etc.) and safety data (adverse events) for each study.

The main outcome was:

a. Pain reduction according to better Visual Analogue Scale of Pain Intensity (VASPI) score

b. Pain relief according to the Categorical Pain Relief Scale (CPRS)

c. Response to treatment (Improvement of pain given by a reduction of >30% of VASPI score without changes in simultaneous opioid use or change in the type of opioid used).

The secondary outcomes were:

a. Frequency of serious adverse events related to treatment with intrathecal ziconotide.

b. Reduction in daily consumption of opioid medication.

Risk of Bias Assessment

One author (JB) evaluated the methodological quality of the selected papers using the risk of bias assessment tool proposed by the Cochrane Collaboration [13]. Additionally the overall quality of evidence for each critical outcome using the GRADE quality assessment criteria [14].

Synthesis of Evidence and Meta-Analyses

We analyzed the data reported in trials for the aforementioned outcomes. The Mantel-Haenzhel method was used to obtain estimates of the Relative Risk (RR) and Risk Difference (RD). We established our type I error in α=0.05 and reported a Confidence Interval of 95% (CI 95%) with every result. We reported the Number Necessary to Treat (NNT) for statistically significant results. All meta-analyses were conducted using the fixed effects model. For meta-analyses, we used the software supplied by the Cochrane Collaboration, RevMan 5.2.

Subgroups and Evaluation of Heterogeneity

We examined heterogeneity and its impact amongst trials with the I^2 value [13]. We considered an I^2 value > 50% as substantial heterogeneity amongst trials. We searched and described the possible causes (differences in trials quality, number of participants, intervention regime, and outcome analysis). When heterogeneity could not be explained or eliminated, we analyzed the data with the random effects model.

The ziconotide high dose vs. low dose subgroup was reported in one trial. The ziconotide vs. intrathecal morphine subgroup is not reported because all trials had a pre-infusion phase (in which all intrathecal opioids were suspended) and the dosage of oral opioids that replaced them was comparable between the intrathecal ziconotide and placebo groups.

Results

The literature search yielded 286 references. Out of these, 14 were preselected, but only three Rauck et al., Wallace et al., Staats et al. met the inclusion criteria and were used for meta-analysis [15-17]. The remaining 11 were excluded, 10 were non-controlled studies such as case series, and one randomized controlled trial that was excluded because it evaluated acute postoperative pain [18-28] (Figure 1).

All studies that describe the effectiveness of ziconotide [15-17] included 595 patients and reported on main and secondary outcomes (Table 1).

Risk of Bias

We found all the included trials to have low risk of bias for randomization, allocation, concealment, complete data at follow-up and intention to treat, with the adequate standardization of observation periods and clear outcomes. However, the authors did not report adequately the method nor the technique of patient randomization and allocation. In addition, only one of the trials Rauck et al. [18] held blinding until completion of the trial, whereas the other two had a crossover phase where blinding was lost and patients from the control group were administered the experimental medication (ziconotide). Therefore, we considered that in their second phase these trials have a high risk of blinding bias and thus were classified as having a "Not Clear" risk of bias for blinding (Table 2).

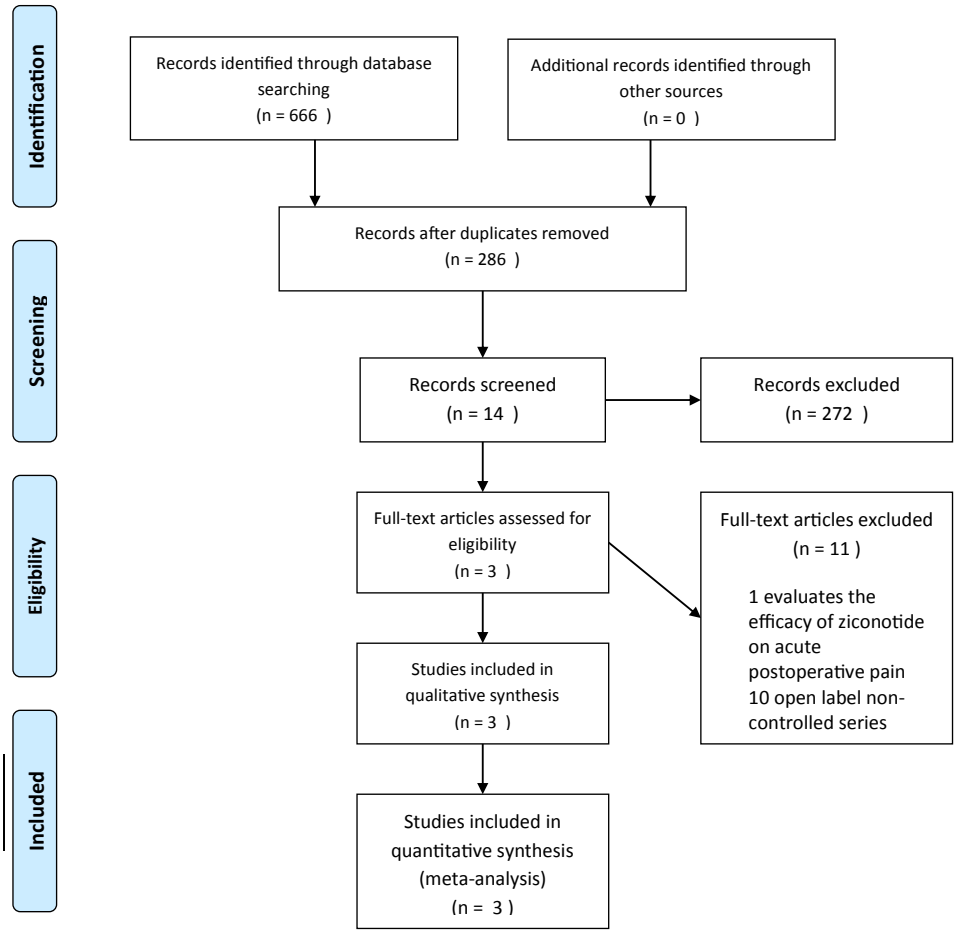

Figure 1: PRISMA Flow Diagram: Literature search and selection

Description of the Randomized Controlled Trials

Detailed descriptions of each of the selected trials regarding population, intervention and outcomes are presented in Table 1. Rauck et al. [18] Prospective double blinded, randomized, controlled trial of two

arms with 220 patients admitted in 39 international centers, 112 are allocated to receive ziconotide and 108 placebo.It evaluates the efficacy and safety ofintrathecal ziconotide with titration of dosage for 3 weeks. Evaluated outcomes were: Pain according to VASPI score, CPRS and McGill scale; quality of life and frequency of adverse events. Loss to follow-up was 8% for the ziconotide arm vs. 4% for the placebo arm. On the first week of treatment there is an improvement of VASPI score of 16.6% for the ziconotide group vs.5% in the placebo group (p=0.0026). On the second week, improvement of VASPI score is 13.8% for ziconotide vs 8.2% for placebo (p=0.12). On the third week the improvement of VASPI score is 14.7% for ziconotide vs 7.2%for placebo (p=0.036). By the end of trial, there is improvement in the satisfaction with the therapy in 28% of patients who received ziconoide vs.12.1% in the patients who received placebo. 17 patients in the ziconotide group and 4 patients in the placebo group achieve improvement according toCPRS (patients who ranked in the upper categories of the scale - Great Relief and Complete Relief). This difference however is not statistically significant (p=0.0596). Reduction in McGill pain scale score is statistically significant(p=0.026). Quality of life measured by the TOPS questionnaire does not demonstrate statistically significant changes (p=0.1837). There is a 23.7%reduction of opioid use in the ziconotide group vs 17.3% in the placebo group(p=0.44) but this difference is not statistically significant. Serious adverse events were dizziness, confusion, ataxia and abnormal gait. These were equally common for both groups (11.6% ziconotide vs 9.3% placebo, p=0.57). Staats 2004: Prospective double blinded, randomized, controlled trial of two arms with 111 patients with AIDS or cancer and VASPI score >50mm are admitted in 32 international centers, 71 are allocated to receive ziconotide and 40 to placebo. Randomization and allocation is done in a 2:1 ratio favoring the ziconotide group. The trial is divided in several phases; the first is the screening phase, which includes removal of intrathecal opioids and the implantation an internal or external intrathecal infusion pump to patients for a total infusion period of two weeks. In the second phase, or titration phase, patients receive ziconotide or placebo for 5 days and those with improvement of pain continue into a thirdstage or maintenance phase for another 5 days. Patients who did not respondto treatment are crossed over to the opposite group for 5 to 6 days loosing blinding. Response to treatment is defined if there is improvement of VASPIscore >30% from baseline without increasing the dosage of opioids. Outcome measures were improvement of pain according to reduction of VASPI, CPRS, Wisconsin Brief Pain inventory (WBPI) and Karnofsky Performance Status Score (KPSS). In the titration phase, there is improvement of VASPI score of 53.1% (CI 95% 44 – 62.2%) with the use of ziconotide vs 18.1% (CI 95% 4.8% - 31.4%) with placebo (p<0.001). In the maintenance phase (n=48) there is a reduction of VASPI score in 69.4% from baseline. 26 patients who crossed over from the control group to the ziconotide group achieve a VASPIscore reduction of 44.9% from baseline. Adverse events are registered according to the number of days from the starting dose of ziconotide and their time of onset, mean dosage at onset and mean cumulative dosage at onset. The most frequent adverse events

Author & Year of Publication	N	M	F	Ziconotide group	Placebo group	Follow Up	Participating centers	Ziconotide Dose	VASPI score improvement	CPRS (Complete Pain Relief or Great Pain Relief)	Serious Adverse Events (SAEs)	Analgesic Response	Opioid Consumption
Rauck et al., 2006	z220	108	112	112	108	3 Weeks	39	Arm 1: 2.4µg/day with titration 1.2 - 2.4µg/ day every 24 hours, maximum dose 21.6µg/day. Arm 2: placebo	VASPI baseline 80.7mm +/- 15. Week 1: Ziconotide: VASPI score improvement 16,6% vs Placebo: 5% (p=0,0026). Week 2: Ziconotide; VASPI score improvement 13,8% vs Placebo: 8.2% (p=0,12). Week 3: Ziconotide: VASPI score improvement 16,1% vs Placebo: 12% (p=0,39)	Ziconotide: 17 patients vs Placebo: 4 patients	Ziconotide: 19 Events (13 patients) vs Placebo: 25 Events (10 patients)	Ziconotide: 45 patients vs Placebo: 27 patients	Ziconotide Group: 23.7% reduction in opioid use vs 17% reduction on the placebo group (p=0,44).
Staats et al., 2004	111	54	54	71	40	2 Weeks	32	Arm 1: 0.1 - 0.4µg/h with titration every 24 hour, maximum dose 2.4µg/h. Arm 2: placebo	Titration phase VASPI score improvement: Ziconotide 53.1% (CI 95% 44% - 62.2%) vs Placebo 18.1% (CI 95% 4.8% - 31.4%) (p<0.001). Maintenance phase (n=48): VASPI score improvement 69.4%, 26 crossing from control group with VASPI score improvement 44.9%	Ziconotide: 36 patients vs Placebo: 7 patients	Ziconotide: 31 Events (22 patients) vs Placebo: 4 Events (4 patients)	Ziconotide: 48 patients vs Placebo: 12 Patients	Ziconotide group: 9.9.% reduction in opioid use vs Placebo: 5.1% increase in opioid use
Wallace et al.,2006	264	143	112	175	89	6 Days	7	Brazo 1: 0.4µg/h entitled according tolerance and response to high dose 7µg/h then reduced to 0.1µg/h y 2.4µg/h, Arm 2: placebo	VASPI score improvement 31.2% (CI 95% 24.6 - 37.9%) Ziconotide vs 6% (CI 95% 0 - 11.9%) Placebo (p<0.001)	Ziconotide 51 pacientes vs Placebo 4 pacientes	Ziconotide: 57 Events (39 titration phase patients) vs Placebo: 3 Events (2 patients)	Ziconotide: 57 patients vs Placebo: 11 patients	There are not any changes in opioid consumption by the end of the trial

Table 1. Efficacy of the Use of Intrathecal Ziconotide Summary of Clinical Data

are dizziness (36 events, mean days toonset 2.5 ± 0.2 days, mean dosage at onset 27.3 µg ± 5), nausea (34events, mean days to onset 2.44 ± 0.3 days, mean dose at onset 0.89 µg/h ± 0.2, mean cumulative dose at onset 34.2 µg ±1), nystagmus (33 events,mean days to onset 2.76 ± 0.2 days, mean dose at onset 1.45 µg/h ± 0.6 and mean cumulative dose at onset 51.3 µg ±19.8), somnolence (17 events,mean days to onset 2.47 ± 0.3 days, mean dose at onset 0.84 µg/h ± 0.2,mean cumulative dose at onset 30.8 µg ± 9.3) and confusion (15 events,mean days to onset 3 ± 0.4 days, mean dose at onset 0.62 µg/h ± 0.1 and cumulative dose at onset 39.8 µg ± 14). Wallace 2006: Prospective double blinded, randomized, controlled trial of two arms which includes 257 patients, 169 allocated to the ziconotide groupand 86 to the placebo group in a 2:1 ratio. These patients had chronic refractory pain, non-neoplasic in origin, refractory to conventional treatment with a VASPI score >50mm. These patients receive treatment for 6 days with a starting dose of ziconotide of 0.4 µg/h titrated upwards until the maximum dose tolerated is achieved (around 7 µg/h). Later, during recruitment the authors had to decrease the starting dose to 0.1 µg/h with a máximum dose of 2.4 µg/h due to adverse events and loss of patients. Reduction of VASPI score from baseline is 31.2% for the ziconotide group vs. 6% for the placebo group (p<0.001). Adverse events are reported on the titration phase for the ziconotide group (gait abnormalities, dyplopia, dizziness, nausea, vomiting and urinary retention).

Ziconotide effects on outcomes

Pain relief according to VASPI score: ziconotide vs. placebo

Pain relief, according to reduction in VASPI score depending on administration of ziconotide vs. placebo is reported in the three included trials. Rauck et al.[2] reported a 14.7% reduction in VASPI scores in the ziconotide group and 7.2% in the placebo group (p=0.036) with a baseline VASPI score mean of 80.7 mm. Staats et al. [19], based on an Intention to Treat (ITT) analysis, reported a 51.4% reduction in VASPI score for the ziconotide group vs 18.1% for the placebo group (CI 95% , 17.3% - 49.4%) (p<0.001) with baseline VASPI score means of 73.6 mm and 77.9 mm, respectively (p=0.18). Wallace et al. 2006 reported a 31.2% reduction in VASPI score (CI 95%, 24.6%- 37.9%) for the ziconotide group vs 6% (CI 95% 0-11.9%) for the placebo group (p<0.001), baseline VASPI score means were 80.1mm for the ziconotide group and 76.9 mm for the placebo group (p=0.029).

According to GRADE tool, the quality of this evidence is moderate due to risk of bias by indirect comparisons between different populations amongst the three trials (Table 2).

Pain relief according to CPRS score

Pain relief according to the CPRS score due to the administration of ziconotide or placebo is reported in the three trials as well. Pain relief was considered when patients were classified as having "Great Relief" or "Complete Relief" in the CPRS scores.The meta-analysis included all the trials Figure. 1 and demonstrated a statistically significant probability of being in the categories of pain relief of the CPRS score when ziconotide was administered (3 trials, 595 patients, RR 4.2 [IC 95% 2.52 - 7.01]; RD 0.21 [CI 95% 0.16 – 0.26]; I^2: 0%; p<0.00001; NNT 5 [IC 95% 3.5-5.9]). Quality of evidence based on the Grade assessment tool is moderate due to risk of bias by indirect comparisons between different populations amongst the three trials (Table 2).

Outcome	N° Patients (Trials)	Quality of Evidence (GRADE)	Relative risk (95% CI)
Reduction (VASPI) Score	595 (3 trials)	⊕⊕⊕⊖ **MODERATE**[3] high risk of bias compared	**RR unreported**
Improvement CPRS (Category Pain Relief Scale)	595 (3 trials)	⊕⊕⊕⊖ **MODERATE**[3] high risk of bias compared	**RR 4.2** (2.52 - 7.01)
Analgesic response	595 (3 trials)	⊕⊕⊕⊖ **MODERATE**[1] high risk of bias for blinding	**RR 2.04** (1.55 - 2.7)
Serious adverse events (AEs)	595 (3 trials)	⊕⊕⊖⊖ **LOW**[2] high risk of bias and imprecision	**RR 2.3** (1.54 - 3.43)
Opioid use	595 (3 trials)	⊕⊕⊕⊖ **MODERATE**[1] high risk of bias for blinding	**RR unreported**

[1] Two of the three trials broke their blinding after the titration phase making them incur in risk of blinding

[2] One of the trials showed a RR less than 1 and is the study with the most statistical weight, there is great heterogeneity bet ween trials with possible publication bias

[3] The 3 trials have very different populations so there is risk of direct comparison bias

CI: confidence interval; **RR:** Relative risk.

Levels of evidence according to the GRADE Working Group

High = Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estim ate.

Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low = Any estimate of effect is very uncertain

Table 2. Quality of Evidence (GRADE)

Response to treatment: ziconotide vs placebo

Response to treatment with ziconotide administration or placebo is reported on all three trials. The definition for response to treatment was the same amongst trials and is defined as reduction of >30% in the VASPI score without an opioid dose increase or opioid change.The meta-analysis included all trials (Figure 2) and demonstrated a statistically significant improvement in response to treatment with the administration of ziconotide (3 trials, 595 patients, RR 2.04 [IC 95% 1.55-2.7]; RD 0.21 [IC 95% 0.14-0.29]; I^2:11%; p<0.00001; NNT 5 [IC 95% 3.6-7.4]). The quality of evidence based on the GRADE assessment tool is moderate due to risk of blinding bias in the crossover phase in two of the three trials (Table 2).

Frequency of serious adverse events

All studies reported on the incidence of adverse events in a similar way. They all showed a tendency for higher incidence of adverse events in the ziconotide group, with over 90% of patients reporting any adverse event (Rauck et al.[2]: 92.9% ziconotide vs 82.4% placebo; Staats 2004: 97.2%

ziconotide vs 72.5% placebo; Wallace et al.[20] 2006: 94.6% ziconotide vs 69.6% placebo). However, the presence of serious adverse events, (described across all trials as confusion, nystagmus, ataxia or urinary retention) was less frequent.

The meta-analysis of the three trials Figure. 3 had to be done by subgroup analysis due to the great heterogeneity of the trials, with a funnel plot that can suggest publication bias due to wide data dispersion Figure. 4. This heterogeneity is explained by differences in randomization in one of the trials Rauck et al. [18] which is done in a 1:1 ratio (ziconotide and placebo on equal proportions) compared to the other two trials in which randomization was done in a 2:1 ratio, favoring ziconotide.

The first subgroup Rauck et al. [18] did not demonstrate a statistically significant difference in the incidence of serious adverse events with ziconotide administration compared to placebo (1 trial, 220 patients, RR 0.73 [IC 95% 0.4 –1.25]; RD -0.6 [IC 95% -0.17–0.04]; I^2: does not apply; p=0.25).

The second subgroup (Staats et al. [29] and Wallace et al. [30] demonstrated a statistically significant increase in the risk of presenting a serious adverse event with ziconotide administration compared to placebo (2 trials, 375 patients, RR 6.68 [IC 95% 3.19 – 14.01]; RD 0.31 [IC 95% 0.23-0.38]; I^2: 0%; p<0.0001; Number Needed to Harm (NNH) 4 [IC 95% 2.7 – 4.3]). However, the quality of this evidence is low due to the great heterogeneity of these trials (Table 2).

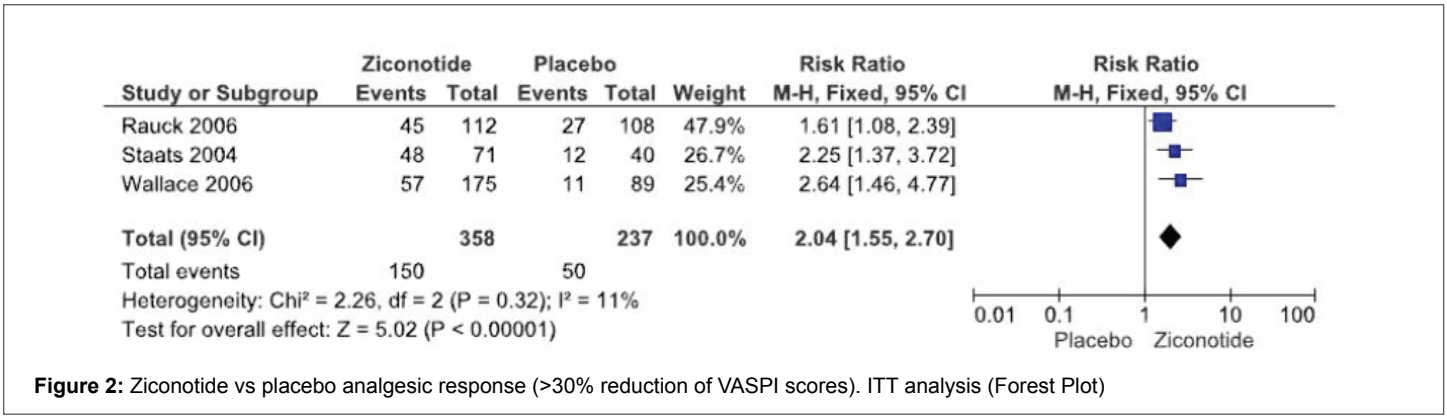

Figure 2: Ziconotide vs placebo analgesic response (>30% reduction of VASPI scores). ITT analysis (Forest Plot)

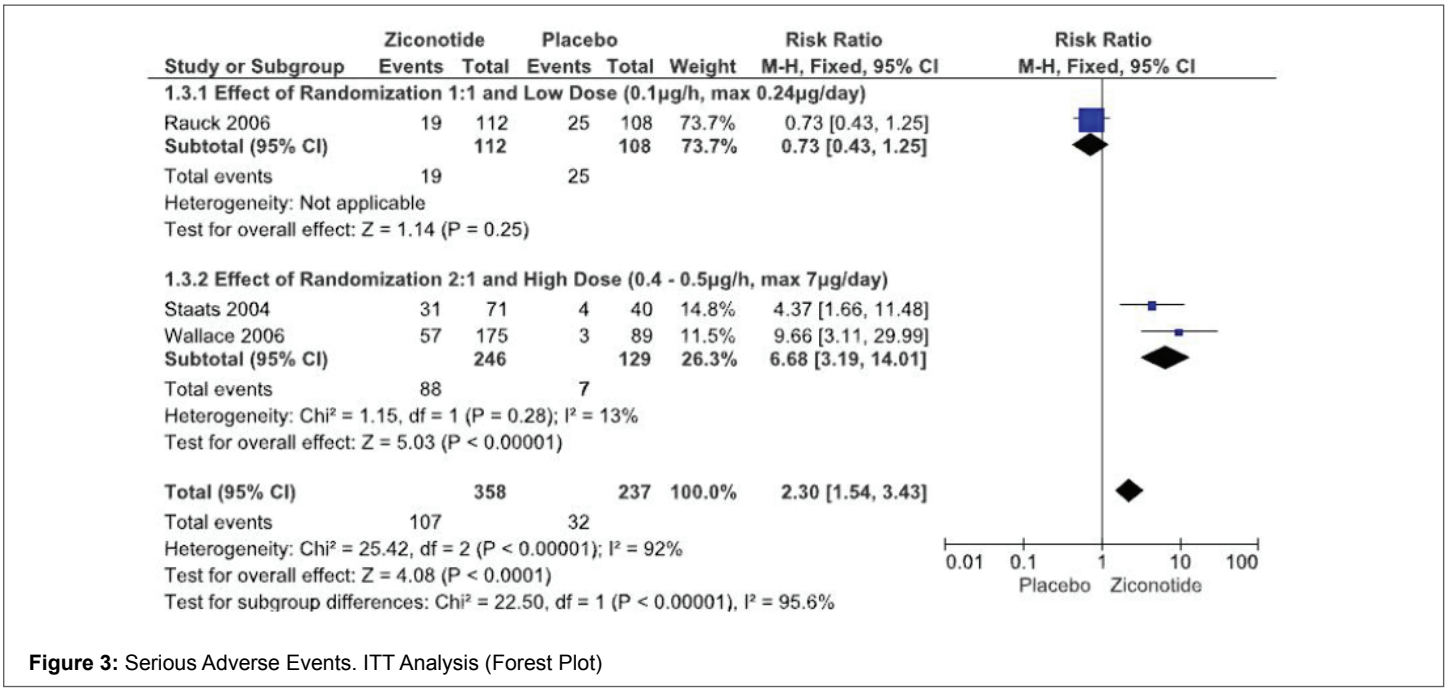

Figure 3: Serious Adverse Events. ITT Analysis (Forest Plot)

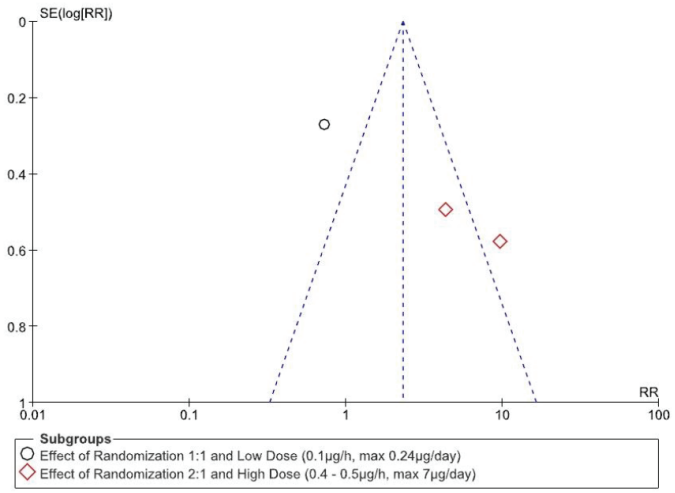

Figure 4: Funnel plot of comparison: Serious Adverse Events (ITT Analysis)

Opioid consumption

Opioid consumption was reported in all included trials. Rauck et al.[18] reported a mean reduction of 23.7% in weekly opioid consumption compared to a 17.3% reduction in the placebo group, although it was not statistically significant (p=0.44). This reduction ranged from 2101 mg (morphine equivalents) prior to treatment to 1524 mg after treatment for the ziconotide group, and from 1876 mg prior to treatment to 1453 mg after treatment for the placebo group.

Staats et al. [19] reported a reduction in opioid consumption of 9.9% for the ziconotide group with a 5.1% increase for the placebo group. Wallace et al.[20] reported that opioid consumption did not change for either group.

The quality of evidence is moderate due to risk of blinding bias in the crossover phase in two of the three trials.

Discussion

Intrathecal ziconotide has been approved as an alternative for the management of severe chronic pain in patients who are intolerant or refractory to other types of analgesic therapy (antineuropathics, opioids, etc.). Furthermore, its effectiveness has been proven by three separated randomized, controlled trials using different types of population. In addition, there are not any established guidelines about the appropriate dosage for pain control without the onset of adverse events. At present, even though there is evidence in the literature [29-34] that supports ziconotide use and dosage, there does not exist a systematic review that summarizes its effectiveness in the management of chronic pain. Moreover, it does not exist either a meta-analysis that quantifies such effectiveness.

This is the first study in which a systematic review of the literature and meta- analysis of prospective randomized, controlled, clinical trials comparing the efficacy of ziconotide vs. placebo for the treatment of severe chronic pain is performed.

Clinical Scores Used for Pain Measurement

There are multiple measures available to assess pain in adult chronic pain populations. To evaluate the multiple dimensions of acute and chronic pain, a number of valid and reliable questionnaires are available.

The Visual Analog Scale for Pain Intensity (VASPI) is a unidimensional single-item scale that provides an estimate of patients' pain intensity. The VASPI is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors, one for each symptom extreme. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be"or "worst imaginable pain" (score of 100 [100-mm scale]). A higher score indicates greater pain intensity. Based on the distribution of pain VAS scores in post surgical patients who described their postoperative pain intensity as none, mild, moderate, or severe, the following cut points on the VASPI have been recommended: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm). Normative values are not available [35]. The Categorical Pain Relief Scale is a unidimensional scale in which patients report their pain intensity and relief according to a 5 categorical scale. It is limited in nature due to inferior sensitivity in comparison with numeric rating scales or the VAS. In-house & Adler (1975) has used both a visual analogue (VAS) and verbal rating scale (VRS) in a double-blind, complete crossover study of analgesics in pathological pain and have found a high correlation between the two scales, although the rating scale in their hands produced more highly significant results in terms of drug differences. They interpreted this to imply that verbal ratings tend to distort by forcing patients to choose a category and that visual analogue scales more closely assessed the patient's experience [36].

Pain relief according to VASPI score reduction

The VASPI score is a quantitative scale designed to minimize the subjective variability of pain. It allows a reproducible and comparable measurement of pain in the clinical environment. The ziconotide use has proven to be superior to placebo in reducing VASPI scores [15-18,20,22,23,37-40], explained by its mechanism of action which consists on direct and selective blockage of N type calcium channels already established by preclinical trials [41-46].

On preclinical experiments, ziconotide has shown that it can be used for neuropathic pain as well as for somatic pain [19]. This feature has been demonstrated in animal models of central sensitization like the paw flinching response in the late phase of the formalin test in mice [20]. The results obtained in our review are consistent with previous studies [7,15-17,21-23,30,38,47]. The low variability of the results regarding this outcome amongst trials suggests that VASPI score reduction is consistent and reliable as a measure of treatment effectiveness. Among the limitations of the analysis of this outcome, we found that the trial's authors did not specified standard deviations nor the VASPI score reduction range.

Pain Relief according to CPRS

Pain relief according to the CPRS score demonstrated an important and statistically significant difference in favor of administering ziconotide over placebo. In the measurement of this outcome figure 1), all three trials were quite homogenous, although the statistical power of each trial on the effect of the intervention has to be weighted. In 2 of the 3 studies (Staats et al. [19] and Wallace et al.[20]), randomization was performed in a 2:1 ratio in favor of the ziconotide group. The authors mentioned that this was done to readily identify the appearance of adverse events and determine the safety dose of ziconotide. However, the trials statistical power is reduced to 0.925 while the established standard power in clinical trials is 0.95. This occurs because this type of randomization allocates 66% of patients from the sample in the ziconotide arm 48, therefore, Staats' et al. and Wallace et al.[20] trials can diminish the real effect of ziconotide. However, we consider the CPRS score as a reliable measure of the effectiveness of ziconotide with an NNT of 5 to obtain benefit from the medication.

The comparative power of our study is limited because the selected trials are the only ones in the literature that have as a secondary outcome relief in pain according to CPRS but it leaves a precedent in the literature as point of reference for future trials.

Analgesic Response: ziconotide vs. placebo (Improvement >30% of VASPI Score)

In the present meta-analysis figure. 2 we demonstrate a statistically significant difference regarding analgesic response in favor of intrathecal ziconotide. The heterogeneity of the trials is low which makes analysis easier and confers security and consistency in the results. The NNT is 5 to achieve an analgesic response.

Our results are consistent with prior systematic reviews and descriptive case series [7,21,22, 25,27,30, 31,32, 34,38, 47,49,50] which demonstrate an adequate analgesic response in patients who receive intrathecal ziconotide. This response to pain is attributed to its mechanism of action as a selective type N channel blocker, limiting the neuronal depolarization and propagation of the pain stimulus. However, this outcome is analyzed in three different populations with specific and controlled clinical conditions. A study, which analyzes the effectiveness of ziconotide in an outpatient clinic environment, with non-controlled conditions and its interaction with other molecules is still lacking.

Safety: The serious adverse events in the analyzed trials were ataxia, nystagmus, somnolence, confusion and urinary retention. Our meta-analysis was done by subgroup analysis due to the great heterogeneity of the results. This is also explained by protocol differences of dose titration in two of the three trials Staats et al.[19] and Wallace et al.[20].

a. The serious adverse events in the analyzed trials were ataxia, nystagmus, somnolence, confusion and urinary retention. Our meta-analysis was done by subgroup analysis due to the great heterogeneity of the results. This is also explained by protocol differences of dose titration in two of the three trials (Staats 2004 and Wallace 2006).

b. Besides the differences in starting dose of ziconotide, there was also variability regarding sample randomization in all trials. This is why Rauck et al.[18] is the trial with greater statistical weight in our meta-analysis figure 3.Thus, in Rauck et al.[18] there were no statistically significant differences in serious adverse event onset with the administration of ziconotide vs. placebo, but in the other two studies there is a marked increase in the risk of having a serious adverse event with the administration of ziconotide (up to 6 times more compared to placebo).

Our results are consistent with previous safety trials [6,11,18,21,22,29,30,43,51-53] Nevertheless, there are also case reports in the literature about the onset of infrequent but serious adverse events with devastating consequences such as psychiatric disorders with risk of suicide [53-55] cardiovascular toxicity [8] or dyskinesia [56] which are not reported in the three trials selected for our meta-analysis.

The quality of the evidence (Table 3) in this regard is low because of the great heterogeneity of results and the non-comparable populations, which in some cases could have been more prone to presenting adverse events, such as the Staats et al.[19] population.

Opioid Use

All three trials had a pre-infusion phase in which all intrathecal medications were withdrawn to included patients, achieving pain control with systemic or oral opioids. However, in spite of pain relief achieved with ziconotide administration, none of the trials demonstrated an opioid use reduction, although Staats et al.[19] reported such a tendency, it was not statistically significant.

Limitations

Unlike previous systematic reviews which are not specific [29-34], our study is the only systematic review, which includes exclusively randomized, double-blind, controlled clinical trials with the objective of quantifying the effect of ziconotide with the use of a meta-analysis. This restriction limits the number of included studies and can affect the statistical power of the meta- analysis. Nevertheless, these restrictions in our study allow us to select trials with evidence level I and II making our analysis less prone to bias.

To avoid publication bias, we performed an extensive search of the literature, including gray literature and abstracts of papers not yet published but presented to the North American pain societies. With this search we found there is only one meta-analysis, which sought to answer the question about the efficacy and safety of ziconotide use for chronic pain but there is no publication of this trial in any database [57]. It is likely that it was published in some non-indexed source of information to which we do not have access.

The quality of evidence for most outcomes was moderate because all trials incurred in at least one limitation or bias, which reduced their epidemiological quality according to the GRADE tool. This is more notorious in the safety outcome where the great heterogeneity of the results given the differences on initial dosing and the effect of randomization, which favored ziconotide, reduced the statistical power of the trial and maximized the frequency of adverse events.

We can also observe that there are no studies that compare the efficacy of intrathecal ziconotide to intrathecal morphine, which is considered the opioid of choice for intrathecal infusion. Furthermore, no long term randomized, double blind, placebo-controlled trials that assess ziconotide effectiveness under daily clinical conditions exists.

Conclusions

Our analysis demonstrated that intrathecal ziconotide is superior to placebo in the management of refractory chronic pain with adequate pain control from different types of patients (AIDS, cancer, neuropathic pain). However, this drug is associated with an increased number of adverse effects such as somnolence, nystagmus, ataxia, or psychiatric disorders. The quality of evidence for this outcome is low which is why further research may be warranted.

Acknowledgement

Maria Ximena Rojas,Doctor in Public Healthcare and Methodology of Biomedical Research Master in Clinical Epidemiology, Associate Professor.

Author Contributions

All authors have worked in preparing the document, discussed the results and commented on the manuscript accepting this as a final form.

This work has been funded entirely by the Hospital Universitario San Ignacio and the Faculty of Medicine of the Pontificia Universidad Javeriana.

Conflict of Interest

We state that we do not have any conflicts of interest regarding any pharmaceutical company, nor have we received any benefit from our work.

References

1. Van Hecke O, Torrance N, Smith BH (2013) Chronic pain epidemiology and its clinical relevance. Br J Anaesth 111: 13-18.
2. Rauck R L, Wallace S M, Allen B W, Leonardo K, James N M (2009) Intrathecal Ziconotide for Neuropathic Pain: A Review. Pain Practice 9: 327-337.
3. Joseph G McGivern (2007) Ziconotide: A Review of its Pharmacology and Use in the Treatment of Pain. Neuropsychiatr Dis Treat 3: 69-85.

4. Turk D, Okisuji A (2000) Bonica's Management of Pain Philadelphia: Lippincott Williams and Wilkins, Pain Terms and Taxonomies of Pain. 3rd edition, 20-27.

5. Hernandez J, Moreno C (2006) Dolor neuropático: La gran incógnita. En: Dolor Neuropático: Fisiopatología, Diagnóstico y Manejo. Bogotá: Editorial Universidad del Rosario 20-30.

6. Acevedo JC (2005) Diagnóstico y Tratamiento del Dolor Neuropático Crónico. Neurociencias en Colombia. 13: 17-25.

7. Acevedo J, Amaya A, de León O, Chinchilla N, de Giorgis M, et al. (2008) Guías para el diagnóstico y el manejo del dolor neuropático: consenso de un grupo de expertos latinoamericanos. Revista Iberoamericana del Dolor 2: 15-46.

8. Wolfe GI, Trivedi JR (2004) Painful peripheral neuropathic and its nonsurgical treatment. Muscle Nerve 30: 3-19.

9. Dworkin R, Backonja M, Rowbotham M Allen RR, Argoff CR, et al. (2003) Advances in Neuropathic Pain. Diagnosis, Mechanisms and Treatment Recommendations. Arch Neurol 60: 1524-1534.

10. Grabow TS, Tella PK, Raja SN (2003) Spinal cord Stimulation for Complex Regional Pain Syndrome: An evidence-based medicine review of the literature. Clin J Pain 19: 371-383.

11. Mathur SV (2000) Ziconotide: A New Pharmacological Class of Drug for the Management of Pain. J Crit Care 19: 67-75.

12. Deer T, Krames ES, Hassenbusch SJ, Burton A, Caraway D, et al. (2007) Polyanalgesic consensus conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 10: 300-328.

13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for Systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 62: 1006-1012.

14. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, et al. (2012). Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 62: 1711-1737.

15. Watters WC (2007) North American Spine Society Evidence-based Clinical Guidelines for Multidisciplinary Spine Care.

16. Higgins JPT, Green S (2009) Cochrane Handbook for systematic reviews of interventions Version 5.0.2.

17. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, et al. (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64: 383-394.

18. Rauck RL, Wallace MS, Leong MS, Minehart M, Webster LR, et al. (2006) A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. J Pain Symptom Manage 31: 393-406.

19. Staats PS, Presley RW, Wallace MS, Presley RW, Wallace MS et al. (2004). Intrathecal Ziconotide in the Treatment of Refractory Pain in Patients with Cancer or AIDS: a randomized controlled trial. JAMA 291: 63-70.

20. Wallace MS, Charapata SG, Fisher R, Byas-Smith M, Staats PS, et al. (2006) Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo- controlled clinical trial. Neuromodulation 9: 75-86.

21. Alicino I, Giglio M, Manca F, Bruno F, Puntillo F (2012) Intrathecal combination of ziconotide and morphine for refractory cancer pain: a rapidly acting and effective choice. Pain 153: 245-249.

22. Atanassoff PG, Hartmannsgruber MW, Thrasher J, Wermeling D, Longton W, et al. (2000) Ziconotide, a new N-type calcium channel blocker, administered intrathecally for acute postoperative pain. Reg Anesth Pain Med 25: 274-278.

23. Deer TR, Kim C, Bowman R, Tolentino D, Stewart C, et al. (2009) Intrathecal ziconotide and opioid combination therapy for noncancer pain: an observational study. Pain Physician 12: E291-296.

24. Dupoiron D, Bore F, Lefebvre-Kuntz D, Brenet O, Debourmont S, et al. (2012) Ziconotide adverse events in patients with cancer pain: a multicenter observational study of a slow titration, multidrug protocol. Pain Physician 15: 395-403.

25. Ellis DJ, Dissanayake S, McGuire D, Charapata SG, Staats PS, et al. (2008) Continuous Intrathecal Infusion of Ziconotide for Treatment of Chronic Malignant and Nonmalignant Pain Over 12 Months: A Prospective, Open-label Study. Neuromodulation 11: 40-49.

26. Mohammed SI, Eldabe S, Simpson KH, Brookes M, Madzinga G, et al. (2013) Bolus intrathecal injection of ziconotide (Prialt®) to evaluate the option of continuous administration via an implanted intrathecal drug delivery (ITDD) system: a pilot study. Neuromodulation 16: 576-581.

27. Raffaeli W, Righetti D, Sarti D, Balestri M, Ferioli I, et al. (2010) Ziconotide: A rapid detoxification protocol for the conversion from intrathecal morphine--the Raffaeli Detoxification Model. J Opioid Manag 7: 21-26.

28. Raffaeli W, Sarti D, Demartini L, Sotgiu A, Bonezzi C, et al. (2011) Italian registry on long-term intrathecal ziconotide treatment. Pain Physician 14: 15-24.

29. Wallace MS, Kosek PS, Staats P, Fisher R, Schultz DM, et al. (2008) Phase II, open-label, multicenter study of combined intrathecal morphine and ziconotide: addition of ziconotide in patients receiving intrathecal morphine for severe chronic pain. Pain Med 9: 271-281.

30. Wallace MS, Rauck R, Fisher R, Charapata SG, Ellis D, et al. (2008) Intrathecal ziconotide for severe chronic pain: safety and tolerability results of an open-label, long-term trial. Anesth Analg 106: 628-637.

31. Webster LR, Fakata KL, Charapata S, Fisher R, MineHart M (2008) Open- label, multicenter study of combined intrathecal morphine and ziconotide: addition of morphine in patients receiving ziconotide for severe chronic pain. Pain Med 9: 282-290.

32. Burton AW, Deer TR, Wallace MS, Rauck RL, Grigsby E (2010) Considerations and methodology for trialing ziconotide. Pain Physician 13: 23-33.

33. Goel S, Grabois M, Aranke S (2012) Safety and efficacy of intrathecal ziconotide: a literature review. J Pain 13: S6.

34. Lynch SS, Cheng CM, Yee JL (2006) Intrathecal ziconotide for refractory chronic pain. Ann Pharmacother 40: 1293-1300.

35. Pope JE, Deer TR (2013) Ziconotide: a clinical update and pharmacologic review. Expert Opin Pharmacother 14: 957-966.

36. Wallace MS, Rauck RL, Deer T (2010) Ziconotide combination intrathecal therapy: rationale and evidence. Clin J Pain 26: 635-644.

37. Williams JA, Day M, Heavner JE (2008) Ziconotide: an update and review. Expert Opin Pharmacother 9: 1575-1583.

38. Backonja MM (2012) Neuropathic pain therapy: from bench to bedside. Semin Neurol 32: 264-268.

39. Kleiber J-C, Theret E, Rapin A, Giltaire A, Peruzzi P (2013) Ziconotide intrathecal treatment, long-term experience. Ann Phys Rehabil Med 56: e117.

40. Mertens P, Brinzeu A, Polo G, Simon E (2013) Intrathecal Ziconotide (ITZ) For The Treatment of Sublesional Neuropathic Pain In Patients With Spinal Cord Lesions. Stereotact Funct Neurosurg 91: 108.

41. Wallace MS (2006). Ziconotide: a new nonopioid intrathecal analgesic for the treatment of chronic pain. Expert Rev Neurother 6: 1423-1428.

42. Adams DJ, Callaghan B, Berecki G (2012) Analgesic conotoxins: block and G protein-coupled receptor modulation of N-type (Ca(V) 2.2) calcium channels. Br J Pharmacol 166: 486-500.

Citation: Acevedo JC, Becerra JE, Gempeler A, and Caballero J (2016) Efficacy and Safety of Intrathecal Ziconotide for the Management of Chronic Pain. A Systematic Review of the Literature and Meta-Analysis Of Randomized, Placebo-Controlled Trials. J Clin Anesth Manag 1(5): doi http://dx.doi.org/10.16966/2470-9956.120

43. Essack M, Bajic VB, Archer JA (2012) Conotoxins that confer therapeutic possibilities. Mar Drugs 10: 1244-1265.

44. Hama A, Sagen J (2013) Use of naturally occurring peptides for neuropathic spinal cord injury pain. Curr Protein Pept Sci 14: 218-230.

45. Pexton T, Moeller-Bertram T, Schilling JM, Wallace MS (2011). Targeting voltage-gated calcium channels for the treatment of neuropathic pain: a review of drug development. Expert Opin Investig Drugs 20: 1277-1284.

46. Schroeder CI, Craik DJ (2012) Therapeutic potential of conopeptides Future Med Chem 4: 1243-1255.

47. Skov MJ, Beck JC, de Kater AW, Shopp GM (2007) Nonclinical safety of ziconotide: an intrathecal analgesic of a new pharmaceutical class. Int J Toxicol. 26: 411-421.

48. Prommer E (2006) Ziconotide: a new option for refractory pain. Drugs Today (Barc) 42: 369-378.

49. Pocock Stuart J (1996) Methods of randomization. Clinical Trials: A Practical Approach 162-165.

50. Klotz U. Bosch M (2006) Ziconotide--a novel neuron-specific calcium channel blocker for the intrathecal treatment of severe chronic pain--a short review. Int J Clin Pharmacol Ther. 44: 478-483.

51. Webster LR, Fakata KL, Charapata S, Fisher R, MineHart M (2008) Open- label, multicenter study of combined intrathecal morphine and ziconotide: addition of morphine in patients receiving ziconotide for severe chronic pain. Pain Med 9: 282-290.

52. Kapural L, Lokey K, Leong MS, Fiekowsky S, Stanton-Hicks M, et al (2009) Intrathecal ziconotide for complex regional pain syndrome: seven case reports. Pain Prac 9: 296- 303.

53. Mitchell, Alisia A, Sapienza-Crawford, Anne J. RN, Hanley K, et al. (2008). Using ziconotide for intrathecal infusions. Nursing 38: 19.

54. Mitchell AA, Sapienza-Crawford AJ, Hanley KL, Lokey KJ, Wells L, et al. (2013) Administering ziconotide and monitoring patients treated with ziconotide: expert opinions. Pain Manag Nurs 14: e84-94.

55. Poli P, Ciaramella A (2010) Psychiatric predisposition to autonomic and abnormal perception side-effects of ziconotide: a case series study. Neuromodulation 14: 219-224.

56. Obafemi A, Roth B (2013) Prolonged delirium with psychotic features from omega conotoxin toxicity. Pain Med 14: 447-448.

57. Penn RD, Paice JA (2000) Adverse effects associated with the intrathecal administration of ziconotide. Pain 85: 291-296.

58. Heifets BD, Smith SM, Leong MS (2013) Acute cardiovascular toxicity of low-dose intrathecal ziconotide. Pain Med 14:1807-1809.

59. Pozzi M, Piccinini L, Giordano F, Carnovale C, Perrone V, et al. (2014) Dyskinesia caused by ziconotide-baclofen combination in an adolescent affected by cerebral palsy. Reg Anesth Pain Med 39: 172-173.

60. Collins R, Lieberburg I, Ludington E, Howard R (2005) Effectiveness of intrathecal ziconotide in multiple pain etiologies: a meta-analysis of three controlled trials. Pain Med 6: 195.