Retrospective Study

Dilution of Ziconotide for Intrathecal Trial: The Effect of Dilution on the Incidence of Side Effects and Pain Relief: A Single-center Retrospective Case-control Study

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Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 06-14-2024
Revised article received: 09-05-2024
Accepted for publication: 10-01-2024

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Background: The optimal dosing and delivery strategies for intrathecal ziconotide are debated. Previous research suggests that high volume, low concentration dosing techniques may decrease side effects and enhance analgesic effect. Previous studies that have investigated the effects of diluting ziconotide have examined continuous infusions of the medication through an intrathecal pump.

Objectives: This study investigates the trial phase to determine if diluting the bolus dose leads to improved outcomes. The hypothesis of the authors is that the dilution of ziconotide will improve the trial outcomes.

Study Design: This single-center, retrospective, case-control study included 62 patients with chronic pain refractory to conservative therapy who received a one-time intrathecal bolus dose of ziconotide.

Methods: The study included 62 patients who received a single outpatient trial dose of ziconotide. The study was approved by an institutional review board. Data were collected from electronic medical records. Doses ranged from a total of 2.5 µg–5 µg in a volume of 0.5 mL–5 mL. The primary endpoints were the number of patients that achieved significant pain relief (≥ 50%) and the presence or absence of side effects. Statistical analysis was performed using a χ^2 test to evaluate side effects and meaningful pain relief and an unpaired, 2-tailed t test to evaluate pain relief percentage.

Results: There were no differences in side effects experienced by the patients in the Undiluted Group compared to the patients in the Diluted Group (21% vs 25%; $P = 0.679$). There were no differences in pain relief in the Undiluted Group compared to the Diluted Group (59% vs 61%; $P = 0.880$). The mean (SD) pain relief in the Undiluted Group was 46% (± 40%) compared to 51% (± 41%) in the Diluted Group ($P = 0.645$). A power analysis revealed a 68% power to detect a difference between the groups.

Limitations: These results are limited by the accuracy of the chart review and sample size; therefore, additional investigation may be warranted.

Conclusion: This study demonstrates there is no substantial difference between diluted and undiluted bolus doses of intrathecal ziconotide in regard to analgesic effect or side effects.

Key words: Ziconotide, analgesic, chronic pain, calcium channel, spinal cord

Pain Physician 2025: 28:147-154

Intrathecal ziconotide is a nonopioid intrathecal analgesic used for managing refractory chronic pain (1,2). Ziconotide achieves analgesic effect by inhibiting the preganglionic N-type voltage-gated calcium channel receptors on the spinal cord, thus, inhibiting noxious signaling from first order to second order neurons. Ziconotide was approved by the US Food and Drug Administration (FDA) for intrathecal administration in 2004 and has become a popular alternative to intrathecal opioid therapy. The only other FDA-approved medications for intrathecal delivery are morphine and baclofen.

The benefits of ziconotide include its nonopioid mechanism, and the absence of cardiopulmonary depression and granuloma formation. The safety and efficacy of intrathecal ziconotide therapy has been demonstrated in the Patient Registry of Intrathecal Ziconotide Management (PRIZM) and is generally accepted as an appropriate therapy for chronic pain refractory to conservative treatment (3). The widespread use of ziconotide has been limited by the medication's side effect profile and narrow therapeutic window (4). Problematic side effects may include dizziness, confusion, somnolence, ataxia, amnesia, hallucinations, and dysarthria (5,6).

Historically, an intrathecal trial of ziconotide was performed prior to implanting an intrathecal pump and initiating treatment with ziconotide. There are some instances where a trial is not required, and may be unnecessary or harmful. When pre-implant trialing is performed, the method varies and may include a continuous infusion trial or an intrathecal bolus trial. According to the Polyanalgesic Consensus Committee, there is not sufficient evidence to support the use of one trialing method over another (7). There has been concern among experts that bolus trials may be too aggressive, leading to patient side effects and inaccurate conclusions about the patient's ability to tolerate ziconotide as a therapy (8). After experiencing side effects, patients may be excluded from, or elect not to continue with further trials of ziconotide. A consensus statement published in 2005 by Fisher, et al (9) called into question dosing titration recommendations from the ziconotide manufacturer and emphasized the importance of low dosing and slow titration of the medication to optimize tolerability. This was further supported by a randomized controlled trial (10) and a systematic review (11) supporting the benefit of low dosing and slow titration on reducing side effects.

There is evidence that when ziconotide is delivered through an intrathecal drug delivery system, diluting the concentration of the infusion is beneficial in reducing side effects and increasing tolerability of the therapy. A retrospective case series by Lindley (12) in 2021 examined 17 patients with chronic nonmalignant axial spine pain, with or without extremity pain in the postimplant phase. Instead of using the standard manufactured concentration of ziconotide (25 μg/mL), the medication was diluted by a factor of 50 to a concentration of 0.5 μg/mL (12). These patients underwent intrathecal pump implantation and were then started on a regimen of ziconotide 0.5 μg/mL, with a basal rate of 0.024 μg/d and a 0.25 μg on-demand patient administered bolus up to 3 times per day (12). It was hypothesized that a low concentration, high volume infusion, along with rapidly delivered patient-controlled boluses may improve pain outcomes due to a better spread in the cerebral spinal fluid (12). These patients generally tolerated the therapy well (12). The average pain relief was 71%; only 2 patients experienced side effects (12). The 2 side effects were headache after bolus dosing and easy bruising (which was thought to possibly be related to other medications) (12). The use of dilute intrathecal ziconotide infusions was also reported in 2015 by Pope and Deer (13) in the context of a novel flex dosing strategy involving nocturnal flex boluses. The concentrations used were 5 μg–10 μg/mL. Patient outcomes were good with 100% of patients tolerating the therapy at 3 months, 75% at 4 months and 70% at 6 months (13).

To our knowledge, no previous study has investigated the effect of diluting a ziconotide trial dose to determine if a high volume, low concentration trial would lead to improved pain relief, or reduced side effects during the trial phase. Our study aimed to compare patients who received a concentrated dose of ziconotide (2.5 μg–5 μg/mL) to patients who received a diluted concentration (0.5 μg–1.67 μg/mL) to determine if any difference was present.

Methods

Our study was a single-center, retrospective, case-control study. The study included 80 patients who received a single shot, outpatient trial dose of ziconotide (Prialt, TerSera Therapeutics, LLC). It was approved by the an institutional review board (protocol #2204563245); Health Insurance Portability and Accountability Act (HIPAA) waiver of research authorization was obtained. A list of all patients who had undergone an intrathecal ziconotide trial at the Center for Integrative Pain Medicine at West Virginia University from October 2014 through August 2023 was obtained through a schedule review.

The inclusion criteria for this study were age greater than 18 years and chronic pain refractory to conservative therapy. Exclusion criteria were bleeding diathesis, an active infection or currently on antibiotic therapy, poorly controlled psychiatric illness, a history of psychosis, or failure to qualify for an intrathecal trial based on medical and psychological evaluation at the Center for Integrative Pain Medicine.

The outpatient practice setting for this study uses a multimodal treatment paradigm. Services offered through this practice include physical therapy, chiropractic care, massage therapy, dietician services, pain psychology, pain psychiatry, acupuncture, exercise therapy, aquatic therapy, medication management, and a broad scope of injection therapies and advanced spine interventions, including comprehensive neuromodulation options. All patients are considered for a broad scope of treatments as is determined appropriate by the team of providers caring for that patient.

The ziconotide trials were conducted by one of 9 physicians employed by the Center for Integrative Pain Medicine. Each trial consisted of a one-time intrathecal bolus dose of ziconotide, which ranged from a total dose of 2.5 μg–5 μg of medication delivered in a total volume of 0.5 mL–5 mL. The patients were discharged home after the trial and the results of the trial, including percent pain relief and side effects, were collected at the follow-up visit. A retrospective chart review was performed to document the percent pain relief and side effects for each trial. If a patient underwent multiple trials, the most recent trial results were included. A standard template was developed for data mining including yes/no answers regarding the following side effects: hallucinations, significant psychiatric side effects, seizures, and a comment section for any other side effects that were reported.

After the chart review, 2 patients were excluded for loss to follow-up, 8 for inadequate data documentation, and 6 that were deceased. One was excluded due to a fall the day of the procedure, making the results of the trial unclear. One patient was excluded because a post-dural puncture headache confounded the trial results. Sixty-two patients were included in the final analysis.

The primary endpoints were the number of patients that achieved significant pain relief and the number and type of posttrial side effects.

The patients were divided into 2 groups based on the intrathecal bolus dose concentrations that were administered at the time of the trial. The Undiluted Group included all patients who had a trial dose with a concentration ranging from 2.5 μg–5 μg/mL. There were 34 patients in the Undiluted Group; their average concentration was 3.90 μg/mL. This is illustrated in Table 1. The Diluted Group included all patients who had a trial dose with a concentration ranging from 0.5 μg–1.67 μg/mL. There were 28 patients in the Undiluted Group; their average concentration was 1.01 μg/mL. This is illustrated in Table 2.

Table 1. *Concentrations of the Undiluted Group.*

Patient	Dose (μg)	Volume (mL)	Concentration (μg/mL)
1	2.5	1	2.5
2	2.5	1	2.5
3	5	1	5
4	2.5	1	2.5
5	2.5	1	2.5
6	5	1	5
7	5	1	5
8	5	1	5
9	2.5	1	2.5
10	5	1	5
11	2.5	1	2.5
12	2.5	1	2.5
13	5	1	5
14	2.5	1	2.5
15	2.5	1	2.5
16	2.5	1	2.5
17	5	1	5
18	5	1	5
19	5	1	5
20	2.5	1	2.5
21	5	1	5
22	5	1	5
23	5	1	5
24	5	1	5
25	5	1	5
26	2.5	0.5	5
27	2.5	0.5	5
28	2.5	0.5	5
29	2.5	1	2.5
30	5	1	5
31	5	1	5
32	2.5	1	2.5
33	2.5	1	2.5
34	2.5	1	2.5
Average			3.897058824

Statistical Methods

Statistical calculations were performed using Microsoft Excel 2024. A χ^2 test was used to compare the proportion of patients in each group (Diluted vs Undiluted) who experienced meaningful pain relief (≥ 50% improvement) and to compare the proportion of patients in each group who experienced side effects. The difference between the percentage of pain relief reported in each group was further analyzed using an unpaired 2-tailed t test. Finally, a post-hoc power analysis was also performed. Additional baseline categorical variables (i.e., gender) were compared using a χ^2 test and baseline continuous variables (i.e., age) were compared using a t test. A value of $P < 0.05$ was considered significant for all tests. All data are expressed as mean ± SD.

Table 2. *Concentrations of the Diluted Group.*

Patient	Dose (μg)	Volume (mL)	Concentration (μg/mL)
1	5	3	1.666666667
2	5	5	1
3	5	5	1
4	5	3	1.666666667
5	5	5	1
6	2.5	3	0.833333333
7	5	5	1
8	2.5	5	0.5
9	5	5	1
10	5	5	1
11	5	5	1
12	5	5	1
13	2.5	5	0.5
14	5	5	1
15	5	5	1
16	5	5	1
17	5	5	1
18	5	5	1
19	5	5	1
20	5	5	1
21	5	5	1
22	5	3	1.666666667
23	5	5	1
24	2.5	5	0.5
25	5	5	1
26	5	5	1
27	5	5	1
28	5	5	1
Average	1.011904762		

Results

Patient demographic characteristics are shown in Table 3. Metrics assessed, including age, gender, and race were notably similar between groups ($P = 0.166$, 0.141, and 0.353, respectively).

The diagnoses of both groups were also analyzed. The most common diagnosis in both groups was persistent spinal pain syndrome. The next most common diagnoses were type 1 or type 2 Complex Regional Pain Syndrome, radiculopathy, peripheral neuropathy, cancer pain, and chronic low back pain. A comparison of the diagnoses in each subgroup are illustrated in Fig. 1.

This study looked to determine the incidence of side effects, the presence or absence of meaningful pain relief (≥ 50%) and the percentage of pain relief achieved in each group. The differences between the Diluted and Undiluted Groups were not significantly different.

Side effects were noted in 7/34 (21%) patients in the Undiluted Group compared to 7/28 (25%) in the Diluted Group. This is not a statistically significant difference ($P = 0.679$) in the proportion (Fig. 2). Significant pain relief was achieved for 20/34 (59%) patients in the Undiluted Group compared to 17/28 (61%) in the Diluted Group. This is not a statistically significant difference ($P = 0.880$) (Fig. 3).

Regarding the amount of pain relief, the mean (SD) pain relief in the Undiluted Group was 46% (± 40%) compared to 51% ± 41%) in the Diluted Group. This is not a statistically significant difference ($P = 0.645$). The individual percent of pain relief for each patient is listed in Table 4. The comparison of the average pain relief in each group is illustrated in Fig. 4.

The average percent of pain relief in the Diluted and Undiluted Groups were calculated and are compared. A power analysis revealed a 68% power to detect a difference between the groups.

Table 3. *Demographic data of the Undiluted and Diluted Groups.*

	Undiluted	Diluted	*P* Value
Age	58.333	62.750	0.166
Gender (% women)	45.5%	64.3%	0.141
Race (% white)	97.1%	100%	0.353

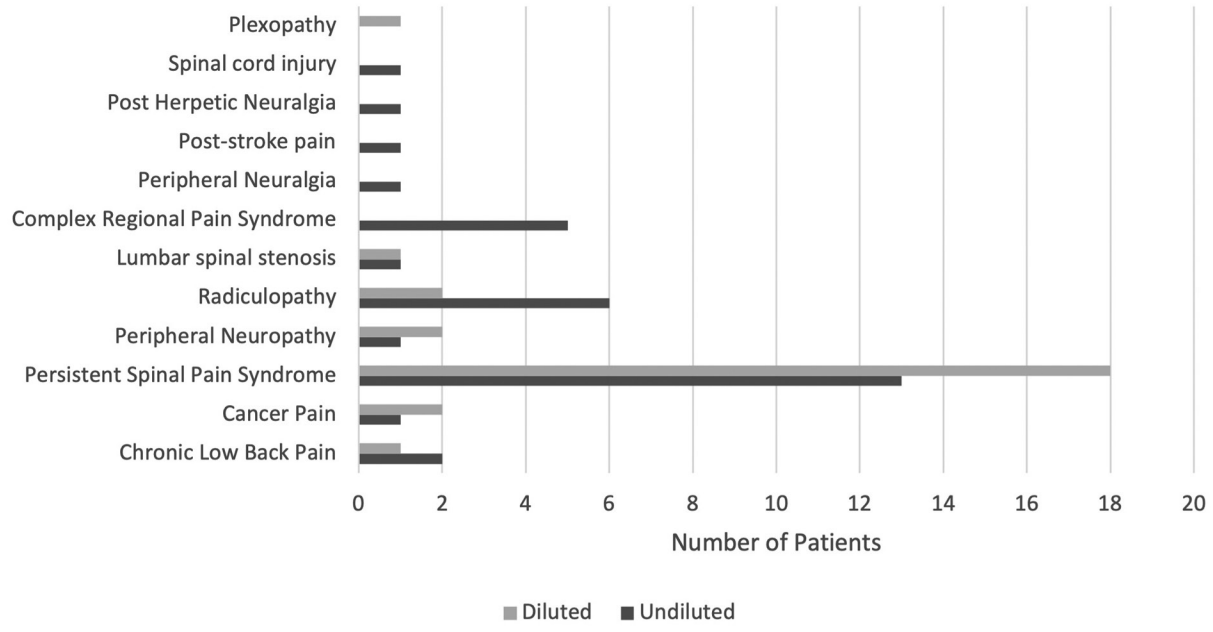

Fig. 1. *Comparative diagnoses in the Undiluted and Diluted Groups. This figure illustrates the number of patients with each diagnosis in both the Diluted and Undiluted Groups.*

Discussion

Sixty-two patients were analyzed in our study. The demographics—including age, gender, and race—were analyzed and no difference was noted. The results of this study showed no significant difference between the Diluted and Undiluted Groups in any of the categories that were investigated (side effects, significant pain relief (≥ 50% benefit) and percentage of pain relief. Side effects occurred in 7/34 (21%) patients in the Undiluted Group compared to 7/28 (25%) in the Diluted Group. A χ^2 test found that this is not a statistically significant difference (P = 0.679). Significant pain relief (≥ 50%) was achieved in 20/34 (59%) patients in the Undiluted Group compared to 17/28 (61%) in the Diluted Group. A χ^2 test found that this is not a statistically significant difference (P = 0.880).

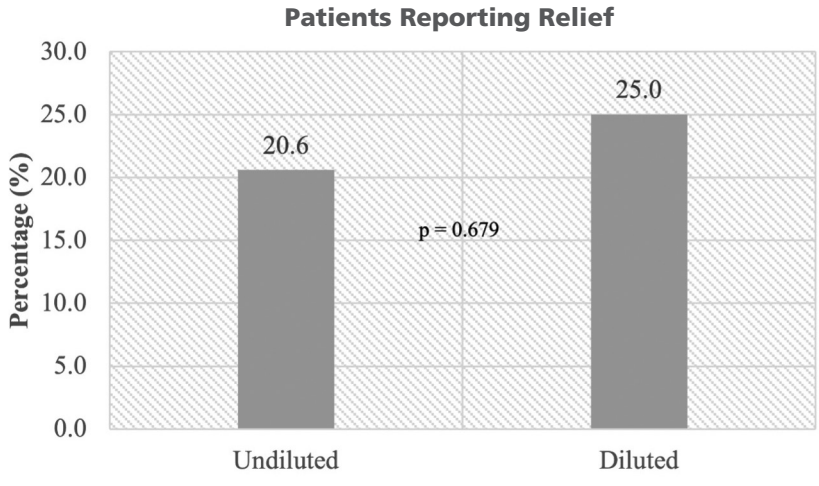

Fig. 2. *Side effects. This figure illustrates the percentage of patients reporting side effects in the Undiluted and Diluted Groups. The P value refers to the statistical analysis done comparing the difference between the 2 groups. P value > 0.*

Regarding the amount of pain relief, the mean (SD) relief in the Undiluted Group was 46% (± 40%) compared to 51% (± 41%) in the Diluted Group. A

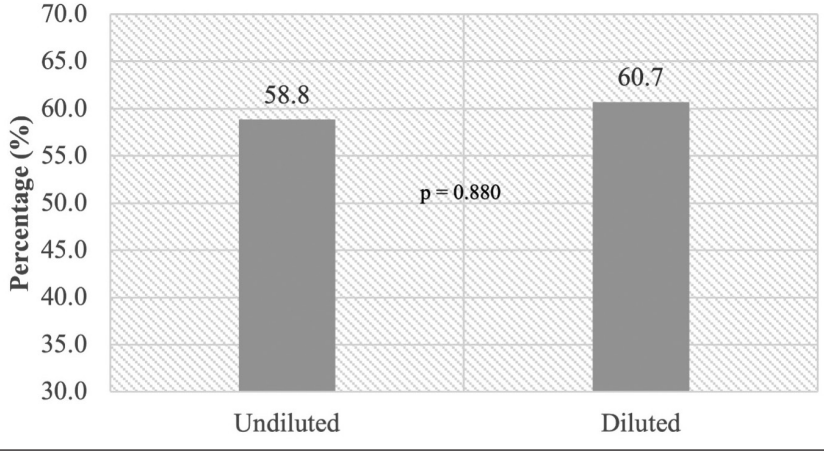

Fig. 3. *Significant pain relief. This figure illustrates the percentage of patients reporting significant pain relief (≥ 50%) from the intrathecal ziconotide trial in each group. The P value refers to the statistical analysis done to compare the difference.*

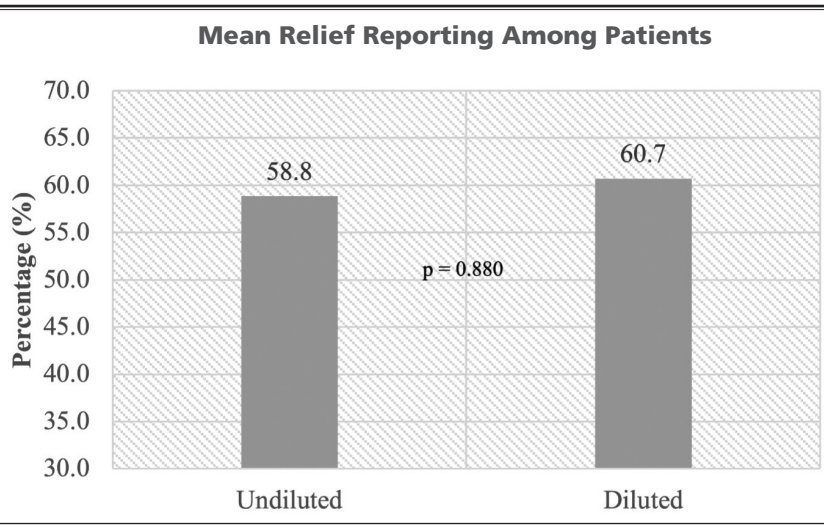

Fig. 4. *Mean percentage relief. The average percent relief in the Diluted and Undiluted Groups.*

2-tailed, unpaired t test demonstrated that this is not a statistically significant difference (P = 0.645). The power analysis demonstrated a 68% power to detect a difference in the amount of pain relief.

The results of our study suggest that diluting ziconotide for intrathecal trial between concentration of 5 µg/mL and 1 µg/mL is unlikely to make a significant difference in terms of side effects, percentage of pain relief, or ability to achieve meaningful pain relief (≥ 50%). our study suggests there is no benefit in taking extra time or resources to dilute this medication prior to an intrathecal trial. This knowledge should help physicians streamline their practice and limit using additional resources. The concern that physicians may be missing patients that could be eligible for intrathecal ziconotide therapy based on trialing too aggressively can be mitigated.

Our study's limitations are that the data collection was limited to what was documented at the time of follow-up. No negative statement confirming the absence of side effects was routinely documented. The chart reviewers assumed that side effects were absent if they were not reported in the follow-up visit note. Another limitation is the possibility of variation in technique among providers. The trials were conducted by one of 9 different physicians, who may all have different techniques, including the possible use of barbotage, which was not documented. Barbotage could potentially affect medication spread and thus trial results. In addition, the only concentrations studied were between 5 µg/mL and 0.5 It is possible that further dilution could be beneficial in reducing side effects. The sample size was strong, but the power was 68%, which may limit the ability of this sample size to detect a difference, if present. Our study did demonstrate that a very large number of patients would be needed to detect a small difference, if present. Finally, a subgroup analysis was not performed.

Recommendations for future studies include further dilutions beyond one µg/mL to determine if higher

volume injectates can reduce side effects. Alternative trial methods could also be investigated, including using barbotage or continuous trials with dilute solutions.

Conclusions

The results of this study suggest that diluting intrathecal ziconotide for the initial trial from 5 μg/mL down to 0.5 μg/mL is not beneficial in improving pain relief or reducing side effects. These results suggest that performing an initial trial at any range between 2.5 μg—5 μg in a concentration of 1 mL–5 mL is generally equivalent. Individual patient doses can then be adjusted based on response, but from a population standpoint, there is no standard concentration at which patients respond best.

Table 4. *Percent pain relief after intrathecal trial for each patient in the Diluted and Undiluted Groups.*

Percent Pain Relief		
Patient	**Undiluted**	**Diluted**
1	0%	90%
2	80%	0%
3	100%	0%
4	100%	90%
5	0%	0%
6	60%	0%
7	70%	85%
8	70%	50%
9	50%	0%
10	0%	60%
11	0	0%
12	0	70%
13	0%	100%
14	100%	0%
15	0%	0%
16	0%	0%
17	60%	80%
18	60%	100%
19	50%	70%
20	30%	98%
21	100%	100%
22	0%	80%
23	100%	75%
24	70%	30%
25	60%	70%
26	90%	75%
27	80%	0%
28	0%	100%
29	0%	
30	90%	
31	0%	
32	75%	
33	70%	
34	0%	
Average	46%	51%

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