ROUND1

Reviewer #1:

Specific Comments to Authors: In general, very interesting paper with very interesting topic. Authors represented novel therapy approach for very hard condition with very high influence on patients quality of life. In my opinion specialists in this field will be interested for this topic. Of course, this is case report and for some scientific conclusion some randomized study with longer follow up period should be done. Very interesting paper with very interesting topic.

Answering Reviewers:Thank you very much for your comments and suggestions. Based on this case, we will conduct a randomized, long-term prospective study in the future to verify the exact efficacy of this therapy.

Reviewer #2:

Q1.You reported a patient with one-year history of severe postherpetic neuralgia who underwent interpeduncular intrathecal catheter insertion followed by continuous infusion of hydromorphone. The patient ’ s pain decreased after intracisternal infusion of hydromorphone. I applaud that the successful management of difficult postherpetic neuralgia. However, the manuscript needs drastic amendments to improve its scientific value. General comments: Scientific manuscripts should provide enough contents for

readers to understand the clinical course of the patient(s) in case report. You need to describe the clinical course of the patient(s) precisely and objectively, avoiding your judgement. When the adopted treatment was effective in a given patient, it should be interpreted that the treatment was effective in the given patient. It is extremely important not to state that the treatment may effective in other pain conditions because you did not study the efficacy of the treatment in other pain conditions.

Answering Reviewers:Thanks for your scientific and careful review, we have revised the paper substantially according to your comments.

Q2.I cannot understand that the patient received “aggressive” medications to treat postherpetic neuralgia, because you did not state the names and doses of medications the patient received.

Answering Reviewers:The pain was rated 7-8 at rest and 9-10 of breakthrough pain(BTP) on an numeric rating scale(NRS), which at first responded to gabapentin（150mg q12 h），oxycodone and acetaminophen tablets (330mg q6h)， and lidocaine 5% patchs(700mg q12 h), but then became refractory to these treatments.

Q3.I would like to recommend that you decide which you would more like to focus on: treatment of postherpetic neuralgia by interpeduncular cisternal infusion of hydromorphone or successful insertion of a catheter into interpeduncular cistern via C3/4.

Answering Reviewers:Our case report focuses on the effectiveness of interpeduncular cistern intrathecal targeted low-dose hydromorphone delivery for intractable craniofacial PHN.

Q4.Specific comments: Abstract: What is your definition of "aggressive?" You need to state the names and doses of medications the patient received. Then, readers would interpret them if the treatment was aggressive or not.

Answering Reviewers:Despite receiving aggressive multimodal therapies including large doses of oral analgesics(gabapentin 150mg q12h，oxycodone and acetaminophen tablets 330mg q6h，and lidocaine 5% patchs 700mg q12 h) and Sphenopalatine Ganglion Block (SGB).

Q5.You did not state the clinical course of the patient satisfactorily after intracisternal hydromorphone. Concise description of clinical course of the patient after hydromorphone treatment is important in your case report. I do not think it has any meaning by stating 0.032mg/day without mention of drug name. You need to state the patient ' s condition preferably six months after stopping intracisternal hydromorphone.

Answering Reviewers:Since the subarachnoid infusion of hydromorphone starts at 1/300 of the daily opioids equivalent dose (oxycodone， 20mg per day)[1]， a continuous daily hydromorphone hydrochloride(Yichang Human-well Pharmaceutical Co.,Ltd, China)

dose was started at 0.064mg/day, and gradually titrated up to 0.128mg/day for improved pain control.

Patient did not report pain or other discomfort at outpatient follow-up 6 months and 1 year after stopping intracisternal hydromorphone.

[1] Sylvester RK, Lindsay SM, Schauer C. The conversion challenge: from intrathecal to oral morphine. Am J Hosp Palliat Care 2004;21(2):143-7.

Q6. Conclusion: You need to state drug names instead of just "opioids." I would recommend that the statement "and other forms… pain." be deleted.

Answering Reviewers:The use of interpeduncular cistern intrathecal infusion with low dose of hydromorphone by IDDS may present an effective alternative in the management of severe PHN.

Q7. Core tip: I would recommend that the statement "This case prove…experience," be deleted.

Answering Reviewers:We discussed the key points and difficulties in the surgical process and the future research expansion of this technique.

Q8.Introduction: You need to state what drugs were used for subcutaneous injection. The expression "Currently, first stage treatments…, as second stage therapies." needs reference.

Answering Reviewers:Currently, first-stage treatments for PHN is medication, followed by the interventional therapies such as botulinum toxin injections, ganglion block，pulsed radiofrequency，nerve or spinal

cord stimulation，as second-stage therapies[2].

[2] Shrestha M, Chen A. Modalities in managing postherpetic neuralgia. Korean J Pain 2018;31(4):235-243.

Q9.You need to state why an intrathecal catheter tip is usually positioned below the level of cranial nerve root entry zone.

Answering Reviewers: ITDD's curative effect validation in the orofacial region is rarely reported in previous study, despite the urgent need of pain relief in patients with craniofacial disorders[3]. And some scholars believe that intrathecal infusion system must be below the neck area[4].Compared with upper cervical routine, the cisternal intrathecal access remains one promising yet rarely applied technique in orofacial pain treatment[3,5]. In view of this, the traditional approach has been to place the intrathecal catheter tip usually below the level of cranial nerve root entry zones, which may lead to an insufficient analgesic effect.

[3] Dupoiron D. Targeted Drug Delivery (Intrathecal and Intracranial) for Treatment of Facial Pain. Prog Neurol Surg 2020;35:181-193.
[4] Gianino JM，York MM，Paice JA，et al． Quality of life:effect of reduced spasticity from intrathecal baclofen. J Neurosci Nurs 1998;30(1) : 47-54.
[5] Narváez MJ, Bulnes JM, Elena JM, et al. Programmable pump for the administration of morphine in the cisterna magna. A new approach. Neuromodulation 2002;5(3):145-9.

Q10.You need to state the region of postherpetic neuralgia instead of just stating PHN.

Answering Reviewers:To provide reference for clinical treatment， the present manuscript aims to briefly describe a case of intrathecal targeted drug delivery by placing the catheter tip near the interpeduncular cistern

for the treatmenting PHN of the ophthalmic branch.

Q11.Case presentation: You need to state permission to publish the case report from the patient.

Answering Reviewers:It is stated at the end of the paper：

Declarations

Consent for publication:Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Q12.History of present illness: You need to state drug names and doses of medications the patient received for readers to understand your meaning of "aggressive medical treatment," which is essential for your manuscript.

Answering Reviewers:The pain was rated 7-8 at rest and 9-10 of breakthrough pain(BTP) on an numeric rating scale(NRS), which at first responded to gabapentin（150mg q12 h），oxycodone and acetaminophen tablets (330mg q6h)， and lidocaine 5% patchs(700mg q12 h), but then became refractory to these treatments.

Q13.Physical examination: Did the patient have "vesicular rash" even one year after the onset of herpes zoster? I do not think Figures 1 and 2 are essential.

Answering Reviewers:Cutaneous scarring on an area of herpes zoster ophthalmicus, hypersensitivity in the ophthalmic division at cranial nerve

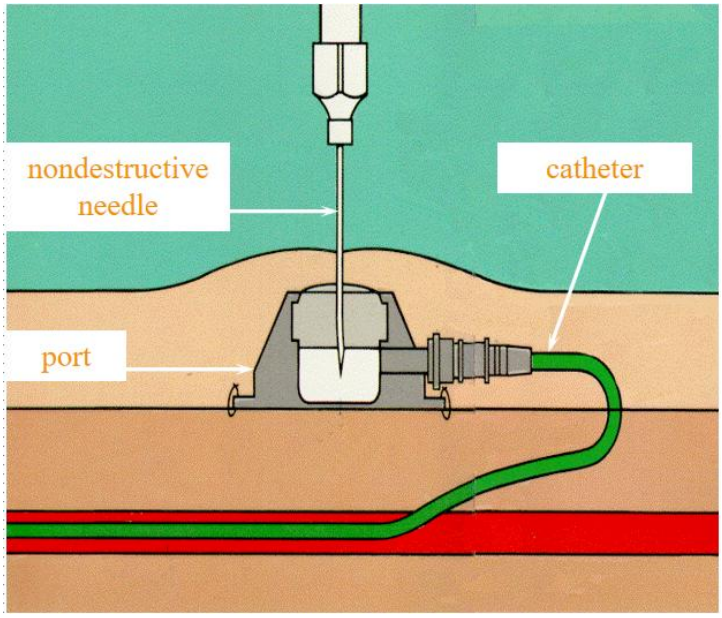
V (trigeminal nerve) distribution, where a light touch can produced pain. Other physical examination results were normal. Figures 1 and 2 have been deleted.

Q14.Treatment: You need to state the patient gave informed consent for the treatment.

Answering Reviewers:The patient gave informed consent for the treatment,and the procedure was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The Characteristic Medical Center of PAP.

Q15.Please explain “nondestructive needle.”

Answering Reviewers:As shown in the figure, the infusion port used for patient treatment is an infusion system buried in the body, which mainly includes an injection seat, a catheter and a professional nondestructive needle. Special nondestructive needle puncture can ensure that the infusion port is used repeatedly, there will be no leakage, and avoid drug extravasation to stimulate the veins. The injection seat can allow 20g non-destructive needle puncture 1000 times and 22g non-destructive needle puncture 2000 times.



Q16.Outcome and Follow-up: One figure that shows doses of hydromorphone and pain levels against time would show your meticulous titration of hydromorphone. I would like to know follow-up study of the patient more than three months after quitting intracisternal hydromorphone.

Answering Reviewers: Patient did not report pain or other discomfort at outpatient follow-up 6 months and 1 year after stopping intracisternal hydromorphone. Figure.2 shows doses of hydromorphone and patient's pain levels against time.

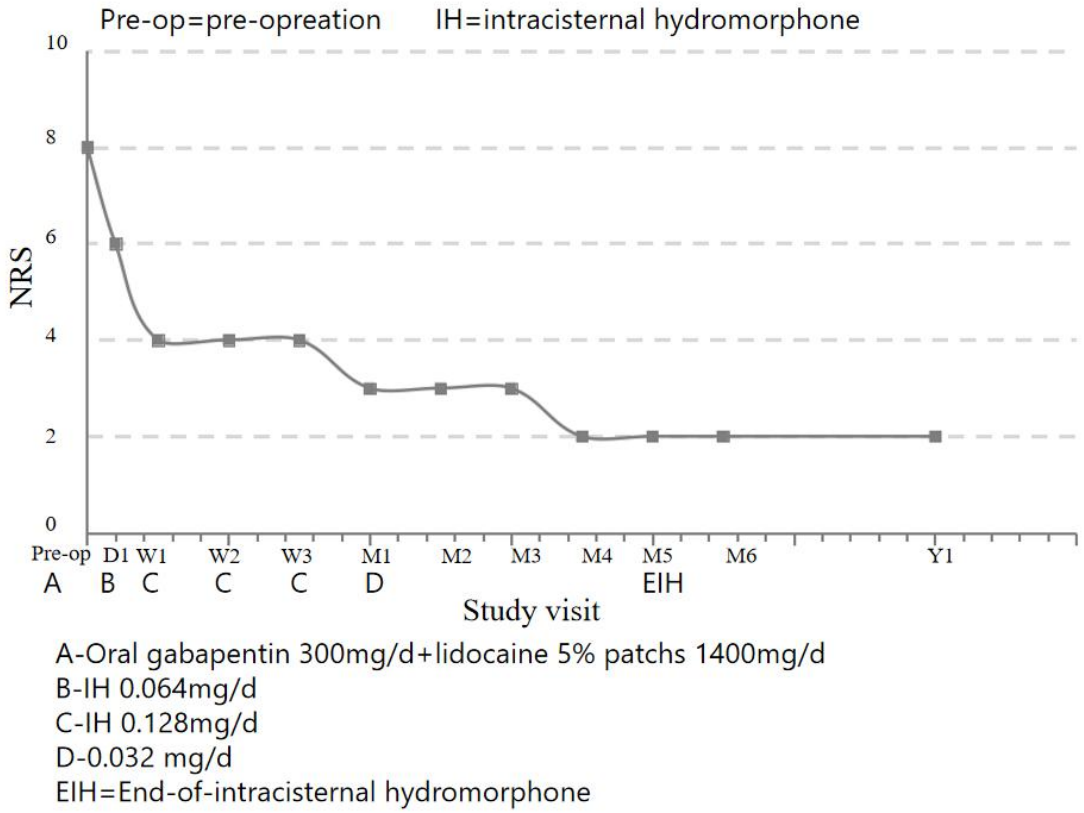


Figure 2. Follow-up of medication dosage and pain level in patient

Q17.Discussion:Are there any reports that studied patients with postherpetic neuralgia with continuous subarachnoid injection of opioids?

Answering Reviewers:To our knowledge, there is few report that studied patients with craniofacial PHN with continuous subarachnoid injection of opioids in the literature.

Intrathecal administration to treat intractable PHN has been proved effective in some studies. Previous studies have reported intrathecal injection of methylprednisolone with local anesthetic or midazolam for the treatment of PHN(Table1)[6]. In addition, several studies have reported intrathecal morphine infusion in the high neck segment for the treatment

of cancer-related craniofacial pain[7-8]. For patients with non-cancer-related pain, intratheca opioids are considered to have Level-3 evidence, a grade B recommendation, and a strong consensus level[9]. Based on the above reasons, our case report focuses on the effectiveness of interpeduncular cistern intrathecal targeted low-dose hydromorphone delivery for intractable craniofacial PHN.

Table 1. Designs of studies using intrathecal injection to treat postherpetic neuralgia.

	Study Design	Inclusion Criteria	Groups	n	Route	Dose	Outcome	Level of Evidence
Kikuchi et al (14)	RCT	Intractable PHN (pain > 1 yr)	IT MP, epidural MP	14, 15	IT, epidural	IT: 3 mL of 2% lidocaine and 60-mg MP; epidural: 5 mL of 2% lidocaine and 60-mg MP (QW*4)	≥ 50% global pain relief: IT 92.3% vs. epidural 16.7% ($P < 0.01$). Persistent reductions in pain, lancinating pain, and allodynia for 24 wks in IT group ($P < 0.005$). Reduced areas of maximum pain and allodynia in IT group ($P < 0.005$).	1b
Kotani et al (13)	RCT, blinded	Intractable PHN (pain > 1 yr)	MP-lidocaine, lidocaine, and no treatment	89, 91, 90	IT	3 mL of 3% lidocaine, 60 mg of MP (QW*4)	≥ 50% global pain relief, with 91% reduction in MP-lidocaine group for 2 yrs ($P < 0.001$). Greater improvement in the severity of burning and lancinating pain, allodynia, and areas of maximal pain and allodynia in the MP-lidocaine group for 2 yrs ($P < 0.001$).	1b
Dureja et al (16)	RCT	PHN with lumbar dermatomes of 3-6 mos duration	Epidural MP, IT midazolam, epidural MP-IT midazolam	50, 50, 50	Epidural, IT	Epidural: 60-mg MP in 10 mL of NS; IT: 2-mg midazolam in 2 mL of preservative-free solvent	VAS for pain and allodynia: ~ 50% pain relief in both IT midazolam groups for 3 wks; persistent relief only in MP-midazolam group for 12 wks. ≥ 50% global pain relief persists for 12 wks in MP-midazolam group ($P < 0.05$). Significant reduction in analgesic use and better quality of sleep in MP-midazolam group.	1b
Rijsdijk et al (15)	RCT	Intractable PHN (pain > 6 mos), VAS score ≥ 4	MP-lidocaine and lidocaine alone	6, 4	IT	MP 60 mg and lidocaine 60 mg or lidocaine 60 mg only (QW*4)	VAS scores for global pain and lancinating pain decreased significantly in lidocaine group. Analgesic use unchanged. *The trial was stopped because of safety concerns and futility of IT MP.	1b

Abbreviations: IT, intrathecal; MP, methylprednisolone; NS: normal saline solution; PHN, postherpetic neuralgia; QOW*4, once every 2 weeks for

[6] Lin CS, Lin YC, Lao HC, et al. Interventional Treatments for Postherpetic Neuralgia: A Systematic Review. Pain Physician. 2019;22(3):209-228.
[7] Moman RN, Rogers JM, Pittelkow TP. High Cervical Intrathecal Targeted Drug Delivery: A Case Report of Refractory Oropharyngeal Cancer Pain. Case Rep Oncol Med. 2019 Sep 10;2019:2098921.
[8] Zou D, Zhang W, Wang Y. Prepontine Cistern Intrathecal Targeted Drug Delivery

for Cancer-Related Craniofacial Pain. Pain Med. 2021 Dec 11;22(12):3112-3114.
[9] Deer TR, Pope JE, Hayek SM, Bux A, Buchser E, Eldabe S, et al. The polyanalgesic consensus conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation. (2017) 20:96–132.

Q18.You stated that "According to clinical experience, the spinal trigeminal nucleus is second order…pain signal centrally." Can clinical experience show that the spinal trigeminal nucleus is second order neuron?

Answering Reviewers:According to the anatomical structure,the spinal trigeminal nucleus is second order neuron to transmits the pain signal centrally[10].

[10] Fromm GH, Chattha AS, Terrence CF, et al. Role of inhibitory mechanisms in trigeminal neuralgia. Neurology 1981;31(6):683-7.

Q19.As the treatment is invasive, you need to mention potential complications related to the procedure.

Answering Reviewers:While we did not observe any obvious complications related to the procedure in this case, potential complications such as arachnoiditis or fungal meningitis, respiratory depression, paresthesia, hemorrhage, surgical site infections, and low-pressure headaches can occur in the perioperative period[11]. Thus, this intervention should be executed with great care and only following completely discussion. Patients should be informed of both the benefits and the potential adverse effects of treatment. Experimental studies of continuous intracisternal injection of opioids are warranted for this often

challenging to treat population and further research in the form of randomized control trials is needed.

[11] Nelson DA, Landau WM, Lampe JB, et al. Intrathecal methylprednisolone for postherpetic neuralgia. N Engl J Med 2001;344:1019-22.

Q20. Last paragraph: I cannot understand the meaning of "puncture of catheter."

Answering Reviewers:Ultrasound-guided puncture appears to be a safety technique for the placement of the catheter, while providing better visualization and no radiation exposure.

Q21.Conclusion: I would recommend that "is" of "…by IDDS is an effective…" be changed to "was." You cannot discuss safety of any treatment, especially invasive one, by one case study. I would recommend that "safe" of "…safe way…" be deleted. I would recommend that "and other forms of… adverse effects." be deleted.

Answering Reviewers:In conclusion, interpeduncular cistern intrathecal infusion with low dose of hydromorphone by IDDS was an effective way to alleviate severe craniofacial PHN.

ROUND2

Number ID 00526025

Reviewer #1:

I applaud you for revising the manuscript satisfactorily in a very

short time. I have enjoyed reviewing your excellent work. I have only one suggestion for you. The content of oxycodone should be stated. END

Answering reviewers: Thank you for your recognition of our work.According to your suggestion, we revise the paper as follows：CASE SUMMARY The pain was rated 7–8 at rest and 9–10 at breakthrough pain (BTP) on an numeric rating scale (NRS). The pain initially responded to gabapentin (150 mg q12 h), oxycodone 5mg/acetaminophen 325 mg q6h, and lidocaine 5% patch (700 mg q12 h), but then became refractory to these treatments. History of present illness The pain initially responded to gabapentin (150 mg q12 h), oxycodone 5mg/acetaminophen 325 mg q6h, and lidocaine 5% patch (700 mg q12 h), but then became refractory to these treatments. OUTCOME AND FOLLOW-UP Subarachnoid infusion of hydromorphone starts at 1/300 of the daily opioid equivalent dose (oxycodone, 20 mg/d); therefore, continuous daily hydromorphone hydrochloride (Yichang Human-well Pharmaceutical Co. Ltd., China) was started at 0.064 mg/d, and gradually titrated up to 0.128 mg/d for improved pain control.