Université de Poitiers
Faculté de Médecine et Pharmacie

ANNEE 2019

THESE

POUR LE DIPLOME D'ETAT

DE DOCTEUR EN MEDECINE

(décret du 16 janvier 2004)

présentée et soutenue publiquement

le 6, septembre, 2019 à Poitiers

par Monsieur Nadeem BEYDOUN

Effectiveness of CT guided epidural infiltration of steroids and local anesthetics for acute herpes zoster and postherpetic neuralgia

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Au **NB²**

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CONTENTS

ABBREVIATIONS

HZ: Herpes zoster

PHN: Post herpetic neuralgia

VAS: Visual analogue scale

VZV: Varicella zoster virus

CT: Computed tomography

SIR: Society of interventional radiology

SD: Standard deviation

INTRODUCTION:

Herpes zoster (HZ) is caused by the reactivation of the latent Varicella zoster virus (VZV) in spinal or cranial sensory ganglia years or decades after primary infection by VZV, also known as varicella (1,2). Among the ninety percent of adults having Varicella, only 20% of them develop HZ (3) representing 3-5/1000 person-years considering all age groups across Europe, North America, Australia and Asia. HZ incidence increases to more than 11/1000 after 50 years of age (3).

Typically, the HZ algia is confined to an area of skin innervated by a single sensory nerve called dermatome. The definition of chronic form, named post herpes neuralgia (PHN) remains debated but is commonly defined as dermatomal nerve pain that persists for more than 90 days after an outbreak of HZ affecting the same dermatome (4). PHN can persist for years (2). It occurs in 10-20% of all HZ patients but in 25-50% after 50 year-old (4).

The European Federation of Neurological Societies presents Level A evidence for both first- and second-line medication therapies to alleviate chronic algia (5). Some interventional treatments were also proposed among them; infiltration by intrathecal or subcutaneous injection of corticosteroid with local anesthetics. Most investigators (Tenicela R 1985, Colding A 1973, Hwang 1999, Pasqualucci 2000, Van Wijck 2006) described infiltration as effective for the relief of acute HZ algia. Hypothesis for corticosteroid and local anesthetics effectiveness would be that HZ virus reactivation leads to neural damage and inflammation with subsequent nervous edema (6). However, in previous studies (7,8), injections were performed without imaging guidance limiting the treatment to accessible dermatome. In addition, complications of peripheral nerve blocks (local injection of anesthetics) and spine infiltrations (local injection of corticoids) are fortunately infrequent but can be devastating. It is commonly admitted that imaging guidance is associated with a lower risk of complication (9). However, to our knowledge, there is no other report evaluating imaging guidance in infiltration for HZ algia.

The purpose of this study is therefore to evaluate the feasibility and the effectiveness of an infiltration by injecting a mixture of steroid and local anesthetic in HZ algia at any stage (acute or chronic) under CT guidance. Six months effectiveness and rate of complications were also studied.

MATERIALS AND METHODS

1. Patients

A monocentric observational study was conducted from April 2017 to February 2019 in one unique center. All patients were prospectively included after giving their informed written consent. This study was conducted according to the International Ethical Guidelines and Declaration of Helsinki.

Inclusion criteria were; patients over 18-year-old, with a proven HZ confirmed by their general practitioner or a dermatologist at an acute or chronic (> 3 months) stage. Exclusion criteria were; disseminated HZ (involvement >2 dermatomes), known immune disorders, patients under 18-year-old, suspicion or state of pregnancy, contra-indication of iodine injection (renal failure, iodine contrast allergy), coagulation disorders, history of surgery at the level of the dermatome (10) and lack of patient informed consent.

Pain was assessed while patients were in the radiology department immediately prior to the infiltration (t0) using a visual analogue scale (VAS) ranging from "0: no pain" to "10: worst pain ever experienced". The follow-up was performed by phone interview at day 7 (t1), at 1 month (t2), 3 months (t3) and 6 months (t4). The VAS score evolution was studied according to time. Potential side-effects were recorded at each call.

Patients also received the standard oral (antivirals and analgesics) prescribed by the patient's physician. Adaptation of the medical treatment during the study inclusion period was possible and the physician was free to adapt the analgesic treatment.

*2. Procedure (**Figures 1,2,3,4**)*

One interventional radiologist with 20 year-experience performed all procedures according to the same protocol. Before the procedure, HZ diagnosis was confirmed by a dermatologist or a general practitioner with a suspected dermatome suggested.

A CT scanner (Somatom Definition AS 128, 2012, Siemens Healthcare, Erlangen, Germany) was used to guide the needle route placement. An initial CT acquisition was performed in a prone position to identify nerve-root level corresponding to the dermatome in cause. After cautious skin disinfection and sub-cutaneous injection of local anesthetics, a 22-gauge needle was inserted to reach the nerve root. Two mL of a

water-soluble nonionic iodine contrast (Iopamiron 200, 200 mg of iodine per milliliter; Bracco, Milan, Italy) was injected to check the good position of the needle and the absence of intra thecal or vascular injection. In case of vascular opacification, the needle tip was replaced.

A pre-curved spinal needle was used in case of complex route. For ophthalmic HZ and for auricular HZ, the target was respectively the trigeminal (Gasser) ganglion in the oval foramen and the C2 sensory ganglion.

After confirming a correct position of the needle, an epidural infiltration was realized by slowly injecting a mixture of two vials of methylprednisolone 40 mg/1ml (*Depo-Medrol**, Pfizer, France), and 2mL of lidocaine 1% (*Xylocaine*,* AstraZeneca, France). Another procedure was performed in case of a VAS decrease less than 20%. No more than 3 procedures at the same level were performed, each separated by at least a month. After the procedure, all patients were clinically monitored for one hour in the department.

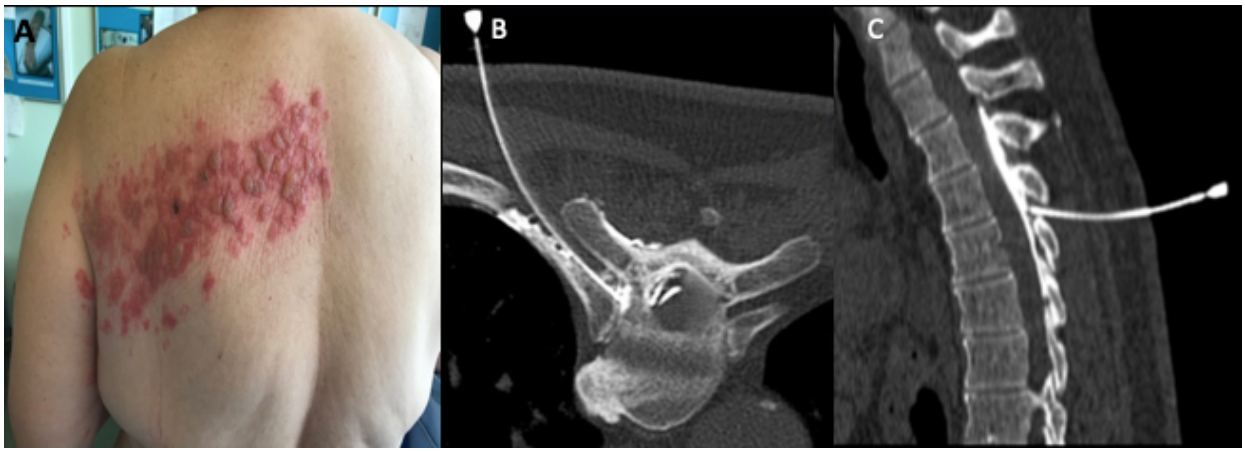
3. Complications

Complications were graded according to the Society Interventional Radiology (SIR) classification (11).

4. *Statistics*

Statistical analysis of VAS evolution over time after epidural infiltration used a linear mixed model of covariance analysis for repeated measurements. This model provided least-square-means estimates and statistical tests for the following effects: time with reference to baseline (t0 of the first procedure, whatever the number of procedures performed), acute vs. chronic algia, and adjustment for VAS value at baseline.

Figure 1



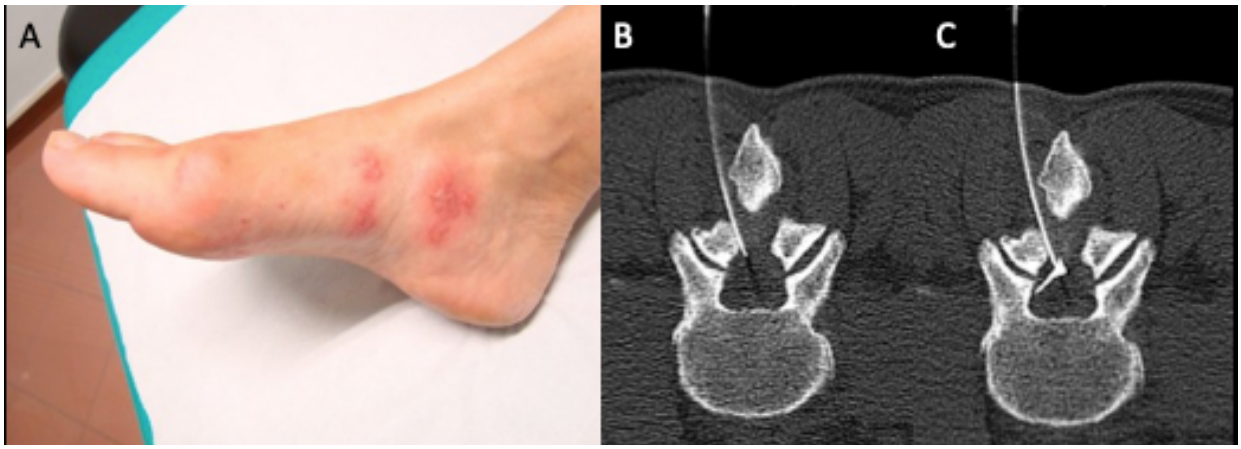
Case of a 70 year-old female patient suffering from an acute herpes zoster.

A: Acute maculo-papulo vesicular skin rash, along the left T2 dermatome.

B: Axial CT showing thoracic epidural injection of contrast performed by using a precurved 22G needle.

C: Contrast spreading two levels on either side of the pathological metamere on sagittal CT.

Figure 2

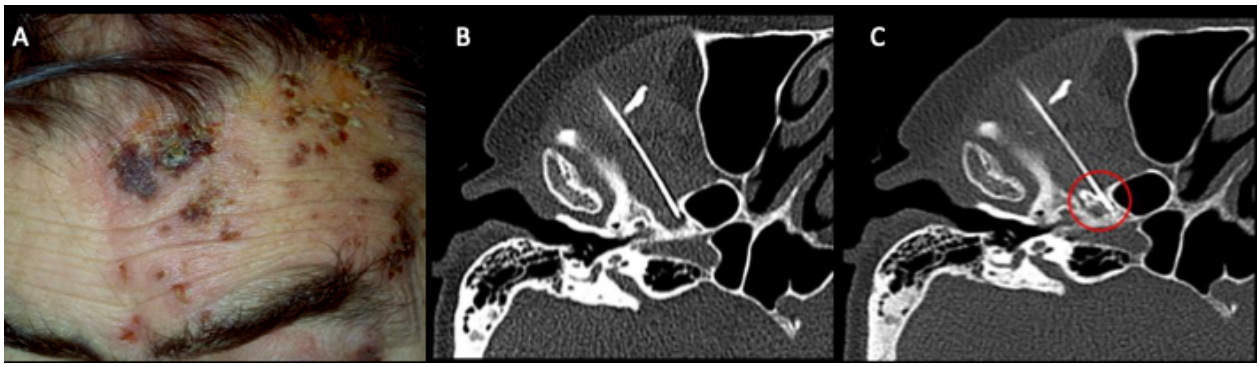


Case of a 68 years old female patient suffering from an acute form of herpes zoster

A: Localized maculo-papulo vesicular skin rash, along the right L4 dermatome.

B and **C**: Axial CT showing inter laminar epidural injection. Note the correct needle position and the absence of vascular injection for a correct L4 lumbar epidural injection.

Figure 3



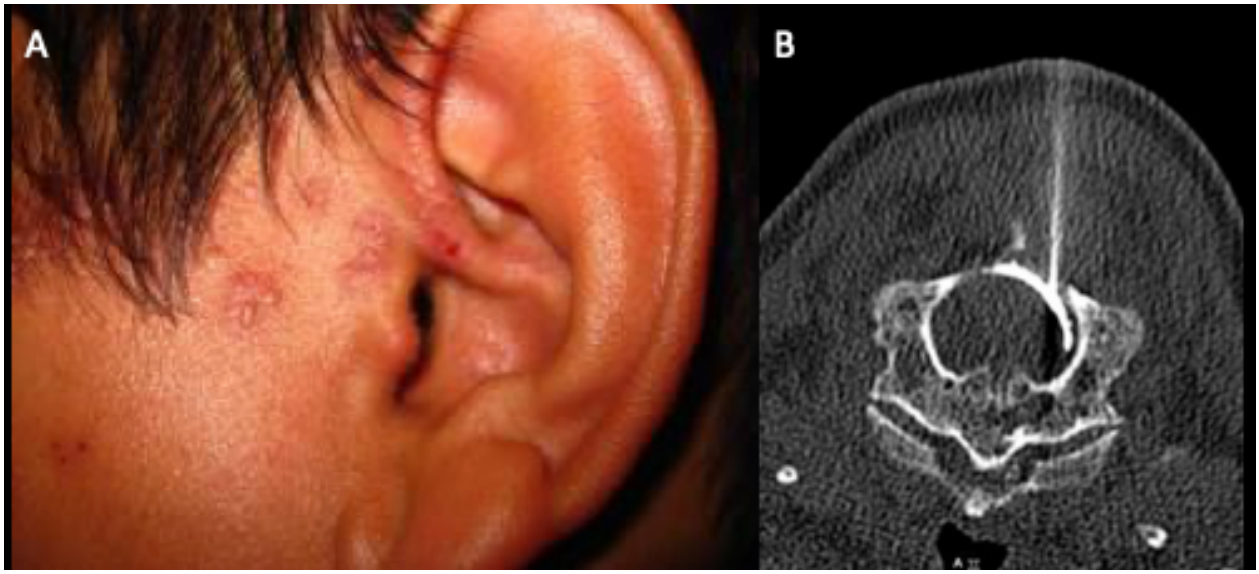
Case of a 82 years old man with a chronic form of a right ophthalmic herpes zoster.

A: Skin rash in the right ophthalmic involving the right part of forehead and eyelid.

B: Axial CT showing the needle tip at the entrance of the oval foramen.

C: Axial CT with contrast injection near the trigeminal ganglion (Gasser's ganglion) confirming the extravascular and extradural position of the needle tip for a correct

Figure 4



Case of a 62 years old male patient with a chronic form of left auricular herpes zoster.

A: Left auricular skin rash (Ramsay Hunt).

B: Axial CT showing a C2 interlaminar epidural injection, with a correct position of the needle tip, localized extra dural and extra vascular.

RESULTS

Twenty patients were finally included. Among the twenty-one patients enrolled, one was excluded after his infiltration because of a withdrawal of consent. Patient demographic and main clinical characteristics are summarized in ***Table 1.***

Compared to VAS before infiltration (8.1 ± 1.2), a significant decrease in VAS score was observed over time ($p<0.0001$) from day 7 (3.4 ± 3.2 $p<0.0001$), until day 180 (2.5 ± 3.1) (***Table 2, and Figure 5***). Differences from baseline did not differ along time ($p=0.72$). The benefit of the epidural infiltration was independent of the initial VAS at t0 ($p=0.51$).

In subgroup analyses, infiltrations were significantly more efficient on acute zona then on chronic pain ($p<0.0001$) and required fewer infiltrations to relieve pain ($p=0.002$) ***(Table 1)***.
The VAS decrease in the acute group, was significant at every time ($p<0.0001$). In the chronic group (N=6), the decrease in VAS was significant at day 7 ($p=0.003$), at day 90 ($p=0.020$), and at day 180 ($p=0.0079$) but not at day 30 ($p=0.062$) ***(Table 2)***.

Among our patients with acute zoster (N=14), 7 of them (50%) still described residual pain at 3 months (mean VAS at 3 months = 4.2), and 5 of them (35%) at 6 months (mean VAS at 6 months = 5.0), corresponding to a ratio of 50% of PHN evolution.

Only one adverse effect was observed; a transient palsy of the lower extremities with total recovery after approximatively 3 hours, graded A in the SIR classification. A medullary MRI was performed and excluded an epidural hematoma. The complication was likely due to unintended perforation of the dura mater with lidocaine.

Table 1: *Patients characteristics*

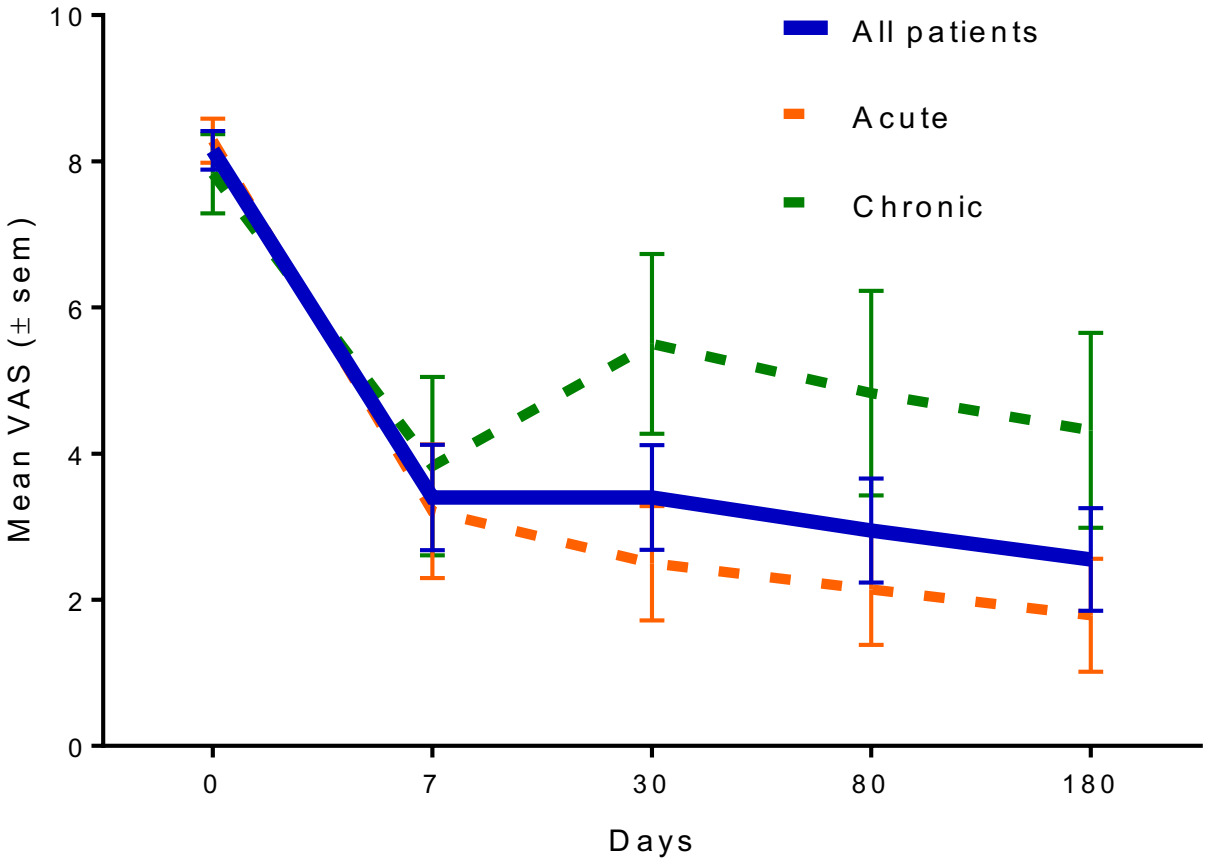
		All patients n=20	**Acute HZ n=14 (70%)**	**Chronic HZ n=6 (30%)**
Gender	*Men, n (%)*	9 (45%)	4 (29%)	5 (83%)
	Women, n (%)	11 (55%)	10 (71%)	1 (17%)
Age	*Year, median (range)*	67 (27-83)	65 (27-78)	68 (37-83)
HZ duration before first injection	*Days, median (range)*	21 (3-5840)	14 (3-80)	488 (110-5840)
Location	*Facial, n (%)*	1 (5%)	0	1
	Cervical, n (%)	4 (20%)	2	2
	Thoracic, n (%)	12 (60%)	9	3
	Lumbar, n (%)	2 (10%)	2	0
	Sacral, n (%)	1 (5%)	1	0
Number of infiltrations	*1, n (%)*	14 (70%)	13 (93%)	1 (17%)
	2, n (%)	3 (15%)	1 (7%)	2 (33%)
	3, n (%)	3 (15%)	0 (0%)	3 (50%)

Table 2: *VAS at different time after inclusion*

Time after inclusion t *(days)*		**All patients n=20**	**Acute HZ n=14**	**Chronic HZ n=6**
t0 *(0)*	*VAS (± SD*)*	8.1 (±1.2)	8.3 (±1.1)	7.8 (±1.3)
	range	6-10	6-10	6-9
t1 *(7)*		3.4 (±3.2)	3.2 (±3.4)	3.8 (±2.9)
		0-10	0-10	0-9
t2 *(30)*		3.4 (±3.2)	2.5 (±2.9)	5.5 (±3.0)
		0-9	0-9	2-9
t3 *(90)*		2.9 (±3.2)	2.1 (±2.8)	4.8 (±3.4)
		0-9	0-9	1-9
t4 *(180)*		2.5 (±3.1)	1.8 (±2.9)	4.3 (± 2.6)
		0-9	0-9	0-8

SD, standard deviation*

***Figure 5**: Mean VAS for all patients, acute and chronic HZ at different time after inclusion*



DISCUSSION

Our results confirm that epidural injections of steroids and local anesthetics combined with standard medical treatment reduce significantly zoster-associated pain at both the acute and chronic stage. The benefit of the epidural injection lasted from day 7 to 6 months. This study shows that CT guidance can be used for correct targeting of the sensitive nerve ganglion.

Complications of epidural injections are fortunately infrequent but can be devastating for both the patient and the physician. It is difficult to obtain reliable data about their real incidence but an incidence of 0.5–1.0 to 10–15% has been proposed (12). Animal studies suggest that intra-fascicular injection with high injection pressures of local anesthetics for neural block could explain neural injury and neurological deficit (13). Spinal ischemia caused by inadvertent injection of corticosteroid into a feeding spinal artery might be another explanation for neural damages (14). As reviewed by Atluri et al., 18 cases have been reported so far at the lumbar level (15). For spine infiltration of corticoids, neural complications may occur as five cases were reported despite CT guidance (9). The number of these complications remains very low compared to the number of lumbar nerve root infiltrations performed.

Nevertheless, imaging guided techniques offer numerous advantages; the first one is a higher success rate. Using ultrasound guidance, Gasparini et al (12) reported a 96% success rate using a nerve stimulator for both upper and lower extremity in 433 patients. Eighty-seven per cent of their catheters were placed on the first attempt, 10% placed on the second, and only 3% placed with more than two attempts. The second is that imaging guidance could minimize the risks of complications (16,17). For that, several precautions must be taken; because the feeding arteries for the spinal cord are usually located anterior and superior, the tip of the needle should be positioned dorsal to the nerve root, and before any injection of medication, a small amount of contrast medium should be administered. The technique presented here respected these rules. Only one adverse effect was observed during this study, graded A based on the SIR classification. In the literature, adverse-effects of infiltrations in HZ algia have been poorly described

(7,8,18). Further studies are therefore required to compare CT guidance and percutaneous approach.

Some authors have proposed continuous infusion of local anesthetic and dexamethasone near a peripheral nerve for the management of pain caused by PHN and acute zoster with a significant effect on pain (19). This technique is also a way to limit the risk of potential iterative punctions. However, despite the benefits and widespread use of continuous infusion, few studies exist regarding the prevention of complications during peripheral nerve catheter placement, management, and removal.

There are limits of this study; it was a single-center study, and the number of participants was relatively small. The follow-up time was limited to 6 months. There are other larger reports showing a significative impact of the infiltration on patient's pain (7,8). Patients inclusion criteria's were heterogenous, as chronic and acute forms were considered, but this reflects the current clinical practice. An accurate list of all treatments received prior to the epidural infiltration was not feasible in our study, especially because of our inclusion criteria's that were heterogenous, including patients with chronic herpes zoster up to 15 years before our treatment. Future studies should include oral treatment follow up and quality of life measures, which have been used in only a few clinical trials of treatments for acute herpes zoster and PHN. Lastly, for acute forms, in a majority of patients, pain usually resolves spontaneously within several weeks. The lack of control group is a real limit considering that epidural infiltrations may appear effective in diminishing pain although pain relief could simply be the result of natural history of the disease. Even though we did not have a control group, the PINE study (7) (randomized controlled trial) which included 598 patients, has shown a significant superiority of epidural injection versus standard medical treatment alone in acute zoster pain.

CONCLUSION

Epidural injection of steroids and local anesthetics under CT guidance in herpes zoster at an acute or chronic stage, provides significant and lasting pain relief. Imaging guidance might be preferred to percutaneous non-guided approach to limit potential risks of the procedure.

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ABSTRACT

PURPOSE:

Evaluate the effectiveness of computed tomography (CT) guided epidural injection of steroids and local anesthetics for acute herpes zoster (HZ) pain and post-herpetic neuralgia.

MATERIALS AND METHODS:

A monocentric study was conducted from April 2017 to February 2019 including patients with HZ algia at any stage (acute or chronic defined as pain lasting more than 3 months). All patients were prospectively included after giving written informed consent. The study was conducted according to the International Ethical Guidelines and Declaration of Helsinki. The sensory ganglion of the affected dermatome and/or the affected sensory nerve was targeted under CT guidance and local injection of a mixture of two vials of Methylprednisolone 40 mg/1ml and 2 mL of Lidocaine 1% was injected. Using a visual analogue scale (VAS) ranging from 0 to 10, pain was assessed prior to procedure, and at day 7, 1 month, 3 months and 6 months. Adverse effects were graded according to the Interventional Radiology (SIR) classification.

RESULTS:

Twenty patients were included (14 acute zoster, 6 chronic). Mean VAS at baseline was 8.2±1.2 with significant decreases ($p<0.0001$) at day 7 (3.4±3.2), day 30 (3.4±3.2), day 90 (3.0±3.2), and day 180 (2.6±3.2). Infiltrations were significantly more efficient on acute zona then on chronic pain ($p<0.001$), and required significantly fewer infiltrations to relieve the pain ($p=0.002$). Only one grade A adverse event was registered.

CONCLUSION:

Epidural injection of steroids and local anesthetics in herpes zoster is feasible, safe and seems to reduce pains with a stable effect over 6 months.

KEYWORDS

Herpes Zoster – Post Herpetic Neuralgia – Infiltration – CT guided interventional procedures

SERMENT

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En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses !
Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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