Pilot Study

A Novel Technique of Saddle Rhizotomy Using Thermal Radiofrequency for Intractable Perineal Pain in Pelvic Malignancy: A Pilot Study

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Background: The prevalence of pain in advanced pelvic cancer may reach up to 95%. Control of such pain is often difficult owing to a variety of neuroanatomical and functional peculiarities. Different modalities have been utilized to treat this pain including saddle chemical rhizolysis with the potential for jeopardizing the neural control of the sphincters.

Objective: The aim of this pilot study is to determine the feasibility of using selective thermal radiofrequency as an alternative to saddle chemical rhizolysis in patients with refractory perineal pain associated with pelvic malignancies.

Study Design: Pilot study.

Setting: Pain Relief Department of the National Cancer Institute, Cairo University.

Methods: Forty patients, 18 years of age or older, who had pelvic malignancy and were complaining of moderate or severe perineal pain not controlled with maximum tolerable doses of morphine sulfate for at least 4 weeks were randomly allocated to receive selective saddle rhizotomy using thermal radiofrequency ablation of S3 on one side and bilateral ablation of S4 and S5 (RF group, n = 20) or conventional chemical rhizotomy using hyperbaric 6% phenol in glycerin (Phenol group, n = 20). Patients were assessed for the intensity of pain, daily consumption of analgesics, functional improvement, overall patient satisfaction, degree of disability and occurrence of procedure-related side effects at 1,4, and 12 weeks.

Result: The results were comparable in both groups regarding the control of pain and functional improvement. The incidence of specific procedure-related adverse outcomes was also equivalent for both interventions, although per-patient incidence of major complications was significantly higher in the phenol group.

Limitation: Small sample size to demonstrate statistical significance of the relatively small frequency of events, and the patients could not be blinded to the intervention they received owing to the technical uniqueness of either intervention.

Conclusion: Selective thermal radiofrequency ablation of the S3 root on one side, S4 root on both sides, and S5 roots could serve as a feasible alternative to conventional saddle rhizotomy using hyperbaric phenol.

Key Words: Perineal cancer pain, chemical rhizotomy, thermal radiofrequency

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In advanced pelvic cancer, the prevalence of pain may reach up to 95% (1). Control of pain associated with pelvic malignancies is often difficult, owing to a variety of neuroanatomical and functional peculiarities unique to this region (2). Of particular concern are the multiplicity of pain generators (whether gastrointestinal,

urogenital, neurological or musculoskeletal), the diversity of the visceral and somatic innervation, and the role of inter-convergence of somatic and visceral afferents in perpetuating and extending the experience of pelvic pain (3,4). Perineal pain is typically a midline experience that requires interventional procedures for pain control to be performed bilaterally.

Different modalities have been tried to treat pain associated with pelvic malignancies including pharmacotherapy and interventional therapy. Saddle chemical rhizolysis using phenol in glycerin have been used through the epidural or subarachnoid space at the sacral region to treat intractable perineal pain associated with pelvic malignancies. Chemical rhizolysis is technically simple and provides acceptable levels of pain relief that usually last for a reasonable duration and may be performed repeatedly in debilitated patients with limited life expectancy (1).

For patients with pelvic or rectal neoplasms, preservation of sphincter function is of paramount concern. The incidence of bladder dysfunction following chemical rhizotomies was reported to be in the order of 1.25% to 24% (5). As early as 1979, Swardlow (6) recommended that, if feasible, neurosurgical selective sacral nerve root rhizotomy to be performed rather than chemical saddle rhizotomy. It is believed that in order to preserve sphincteric control, S2 and S3 have to be kept intact on one side (1). Selective rhizotomy using radiofrequency (RF) or cryoanalgesia is preferred to conventional chemical neurolysis based on the presumed higher safety, selectivity, and controlled lesioning (7).

The aim of the present study is to determine the feasibility of using selective thermal radiofrequency as an alternative to subarachnoid phenol injection for saddle rhizotomy in patients with refractory perineal pain associated with pelvic malignancies. Refractory pain was defined as pain that was not controlled with maximum tolerable doses of opioids and adjuvant analgesics (8).

Methods

This prospective, randomized, controlled, clinical trial was conducted at the National Cancer Institute (NCI), Cairo University, Cairo, Egypt, during the period of June 2016 to July 2017. The study was approved by Institutional Review Board (approval No. 201516026.2) and was registered at ClinicalTrials.gov (NCT03084575).

Our patients were recruited from the NCI pain clinic. All data regarding the technical benefits, expectations and hazards of the procedure were explained to all patients and written informed consent was obtained. Patients 18 years of age or older who had pelvic malignancy with a life expectancy < 12 months (9) and complained of moderate or severe perineal pain (pain score > 40 out of 100 on the standard visual analogue scale) that was not controlled with maximum tolerable doses of morphine sulfate for at least 4 weeks (10) and adjuvant analgesics (pregabalin) were eligible for the study. Patients were excluded if they had contraindication to lumbar puncture (coagulopathy, local or systemic infection, increased intracranial tension) or had advanced malignancy distorting the anatomical landmarks thus rendering the procedure technically difficult or unsafe. Other exclusion criteria were history of allergy to phenol or urinary or fecal incontinence.

Randomization, Allocation and Concealment

Patients were randomly allocated to receive selective saddle rhizotomy using thermal radiofrequency ablation of S3 on 1 side and bilateral ablation of the S4 and S5 (RF group, n = 20) or conventional chemical rhizotomy using hyperbaric 6% phenol in glycerin (Phenol group, n = 20). Patients were randomized using a computer-generated random number, and the random number list was concealed and was accessed immediately prior to patient allocation by personnel not involved in the study.

Interventions

Cefazolin 1 g was given by IV infusion 30 minutes prior to the procedure. Interventions were conducted in the intervention room under standard monitoring including electrocardiography, pulse oximetry, and non-invasive arterial pressure monitoring. Supplemental oxygen was administered via nasal prongs at a rate of 3 l/min and conscious sedation was provided with IV dexmedetomidine boluses at a dose of 0.5 to 1.0 µg/kg combined with IV fentanyl 0.5 to 1.0 µg/kg.

Technique of Thermal RF Rhizotomy

The patient was positioned prone over a radiolucent table. Under fluoroscopic guidance, alignment of the L5-S1 interspace was achieved and then the C-arm was tilted 5-10° ipsilaterally to display the sacral foramina. The S3 foramen was visualized on the dominant side of pain and the S4 foramina were visualized bilaterally. If there was no dominant side of pain, the S3 foramen that was more conveniently accessed was chosen. The S5 roots were traced on lateral view of the

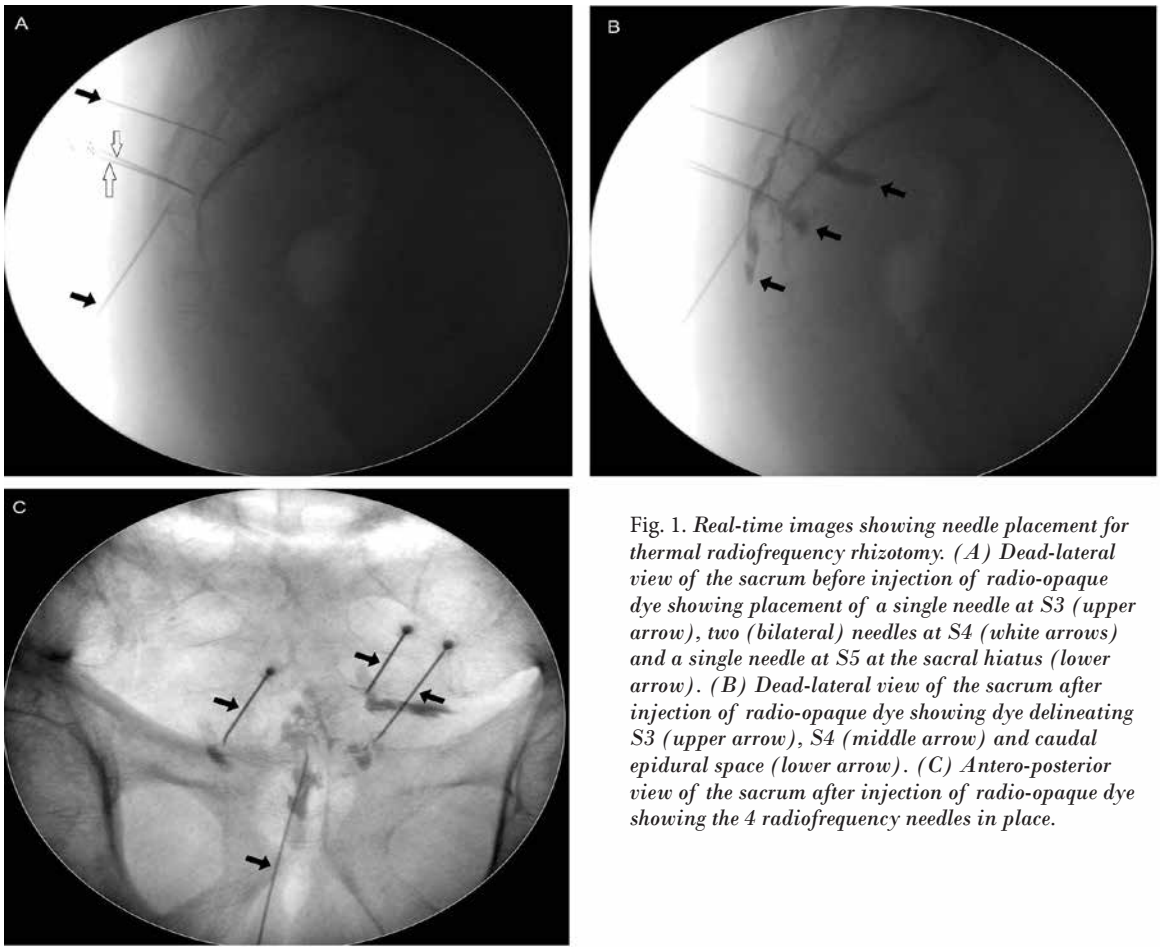

Fig. 1. *Real-time images showing needle placement for thermal radiofrequency rhizotomy. (A) Dead-lateral view of the sacrum before injection of radio-opaque dye showing placement of a single needle at S3 (upper arrow), two (bilateral) needles at S4 (white arrows) and a single needle at S5 at the sacral hiatus (lower arrow). (B) Dead-lateral view of the sacrum after injection of radio-opaque dye showing dye delineating S3 (upper arrow), S4 (middle arrow) and caudal epidural space (lower arrow). (C) Antero-posterior view of the sacrum after injection of radio-opaque dye showing the 4 radiofrequency needles in place.*

sacrum and were located by the operator palpating the bony sacral hiatus. Baylis, curved, sharp-end, 20-gauge, RF needles with 100 mm long shaft and 10 mm long active tip were inserted for thermal ablation of the target roots. Iohexol contrast medium 0.2 mL was injected at each sacral root, then the AP and lateral views were checked for satisfactory spread of the radioopaque dye along the target sacral roots (Fig. 1A through 1C). After sensory (50 Hz, 0.5 to 0.7 V) and motor (2 Hz, 1.0 to 1.5 V) stimulation for verification of proper location of needle tip, 0.75 mL of 2% lidocaine to which 1 mg of dexamethasone is added (making up a total volume of 1 ml) was injected before the delivery of thermal RF lesioning with the needle tip temperature set at 80ºC and applied for 180 seconds. After the procedure, the patient was transferred to the recovery room where they were monitored for 1 to 2 hours before discharge.

Technique of Hyperbaric Chemical Saddle Rhizotomy

The procedure was done with the patient sitting up After surgical sterilization with povidone iodine and draping the procedure area, a 20-gauge Quincke-bevel spinal needle was introduced at the L5-S1 interspace. Loss of resistance to saline was first used to locate the epidural space before advancing the needle further to tap the dura. After obtaining CSF backflow in the spinal needle, the patient is adjusted 30-45 degree, with the patient leaning backward to enhance the spread of the injectate towards the posterior sensory roots before increments of 0.1 mL of 6% phenol in glycerine were injected using a tuberculin syringe while an assistant assessed the patient's pain in the saddle area as well as the movement and sensations of both lower limbs until the desired effect is attained. The volume

to be injected was set at a maximum limit of 0.7 mL in females and 1.0 mL in males. After injection, the patient was kept in the same position for 30 minutes to enhance the concentration of the injectate in the vicinity of lower-most dorsal (sensory) sacral roots (11,12). After the procedure, the patients were transferred to the recovery room where they were monitored for 1 to 2 hours before discharge.

Outcome Measures

The primary outcome measures were the severity of pain, daily consumption of analgesics, and degree of functional improvement. Secondary outcome measures were the overall patient satisfaction, degree of disability, and occurrence of procedure-related side effects.

The severity of pain, daily consumption of analgesics, and degree of disability were assessed before the procedure. Outcome measures were assessed at 1 week, 4 weeks and 12 weeks. Pain was assessed on a standard 100-mm visual analog scale (13). Functional improvement was self-rated by the patient using the scale proposed by Costandi and colleagues (14) which is interpreted as follows: 0% to 25% = minimal improvement, 25% to 50% = mild improvement, 50% to 75% = moderate improvement and 75% to 100% = marked improvement. The cumulative daily consumption of oral morphine sulphate and pregabalin were recorded by the patient in a pain diary and were reviewed at each follow-up visit.

The degree of disability was scored using the Oswestry Disability Index (ODI) (15). Overall patient satisfaction was graded on the Patient Global Impression of Changes scale (PGIC) (16). Procedure-related adverse outcomes were categorized into major and minor complications. Major adverse events included development of sphincteric dysfunction; new motor deficit; or new sensory symptoms including numbness, dysthesia, paresthesia or aggravation of the pain. Minor complications included orthostatic hypotension, post-dural puncture headache, local infection, and backache or hematoma formation.

The outcome measures were assessed by a blinded clinician who otherwise did not participate in the conduct of the study.

Statistical Methods

The required sample size was calculated using the G*Power Software version 3.1.9 (Universität Düsseldorf, Germany). Since there was no previous study comparing the 2 interventions of interest in patients with perineal pain, the current exploratory study targeted an effect size that would be clinically relevant. So, it was estimated that a sample size of 18 patients in either group would have a power of 80% to detect statistically significant difference between the 2 study groups as regards the pain scores and analgesic consumption, the principal outcome measures, for a relatively large effect size equivalent to a Cohen d coefficient of 0.96 (i.e., approximately a standardized mean difference of 1). This calculation used a 2-sided unpaired t test with a type 1 error of .05. Assuming a drop-out rate of approximately 20%, 20 patients were recruited into each study arm.

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Continuous numerical variables were presented as mean and standard deviation or standard error of the mean and intergroup differences were compared using the unpaired Student t test. Categorical variables were presented as ratio or as number and percentage and between-group differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). Mixed linear modeling (MLM) was used to examine the effect of the treatment modality (RF versus phenol injection) on the change in the pain scores and analgesic consumption. Reported P-values are 2-sided. *P*-values < .05 were considered statistically significant.

Results

During the study period, 83 patients were assessed for eligibility. Forty-three (51.8%) patients were primarily excluded. Causes of exclusion were refusal to participate (n = 14, 32.6%) or failure to fulfill eligibility criteria (n = 29, 67.4%). Forty patients (48.2%) were enrolled and were randomized to receive RF (n = 20) or phenol injection (n = 20). None of the included patients were lost to follow-up or secondarily excluded (Fig. 2).

The mean ± SD age was 51.6 ± 13.1 years in the RF group and 50.2 ± 12.7 years in the phenol group with a male/female ratio of 11/9 in both groups. Patients were either cancer–free patients (cured) (3/20 in the RF group and 4/20 in the phenol group), patients under therapy (6/20 in both groups), or patients with advanced disease (11/20 in the RF group and 10/20 in the phenol group).

Mixed linear modeling was done to compare the change in the pain score and analgesic consumption in the 2 groups. There was a statistically significant difference between the two groups in pain scores favoring phenol injection over RF (estimated marginal mean ± SE, 37.8 ± 1.04 versus 41.8 ± 1.04, respectively; *P*-value (.008).

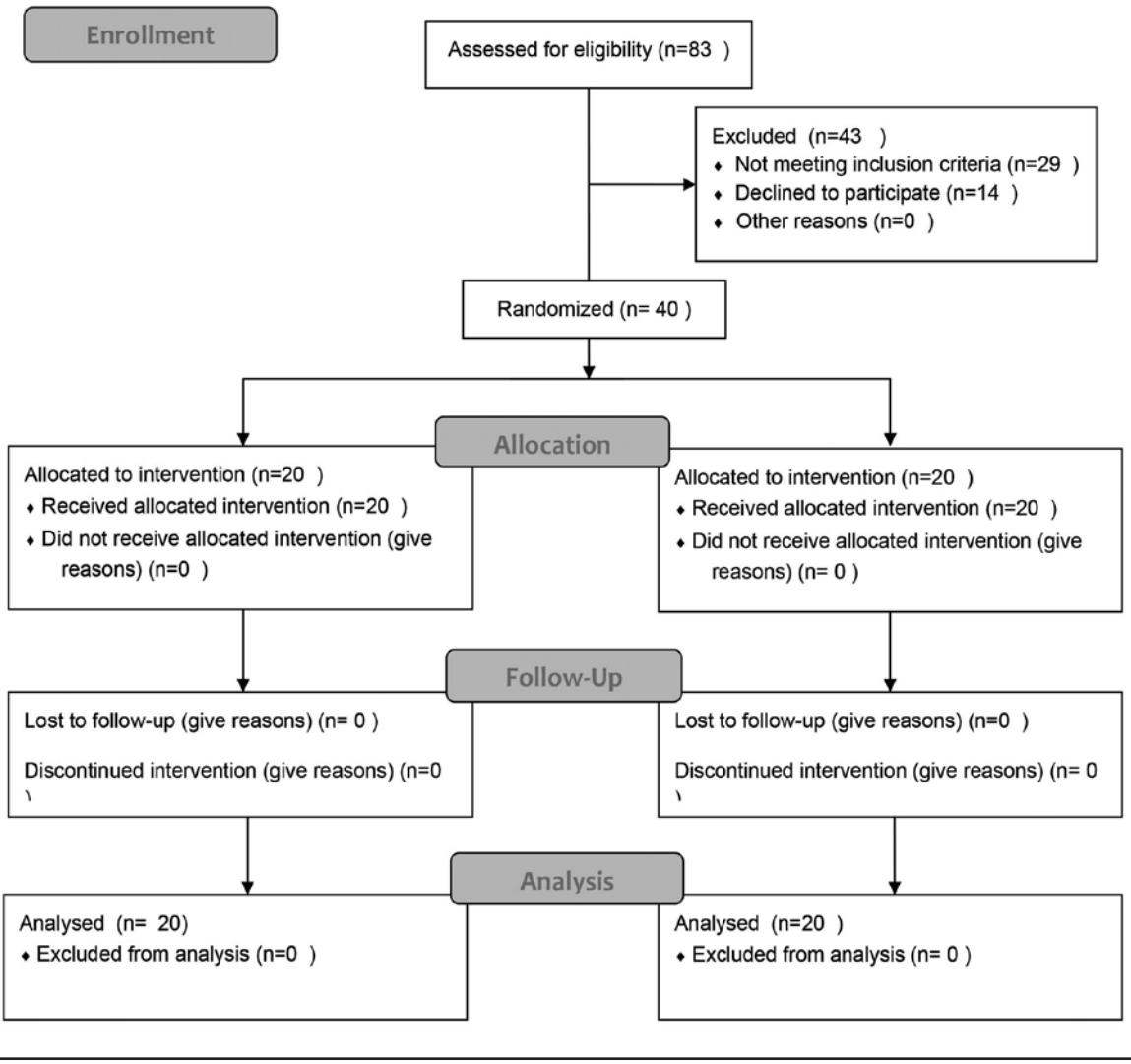

Fig. 2. *Flow chart showing the study flow.*

However, the difference was too small to be of clinical relevance (mean difference, 3.9; 95% CI, 1.04 to 6.8). There was no statistically significant difference between the 2 groups in the daily consumption of morphine (estimated marginal mean ± SE, 49.0 ± 2.7 mg/day versus 49.8 ± 2.7 mg/day for RF or phenol, respectively; *P*-value .847) or in pregabalin consumption (estimated marginal mean ± SE, 145.9 ± 7.0 mg/day versus 136.6 ± 7.0 mg/day for RF or phenol, respectively; *P*-value .347 (Fig. 3).

Both groups were comparable in the functional improvement outcome (Table 1), change in the ODI (Table 2) and the incidence of specific procedure-related adverse outcomes (Table 3). However, the per-patient incidence of major adverse outcomes was significantly higher in the phenol group (25% versus 0%; *P*-value .047) (Table 3).

Regarding the patients' rating of their satisfaction with the outcome of the procedure, The differences were not statistically significant (*P*-value .847) (Table 4).

Discussion

Management of cancer-related perineal pain comprises a challenge to the pain practitioner owing to the complexity of the innervation of this region (2, 17). In

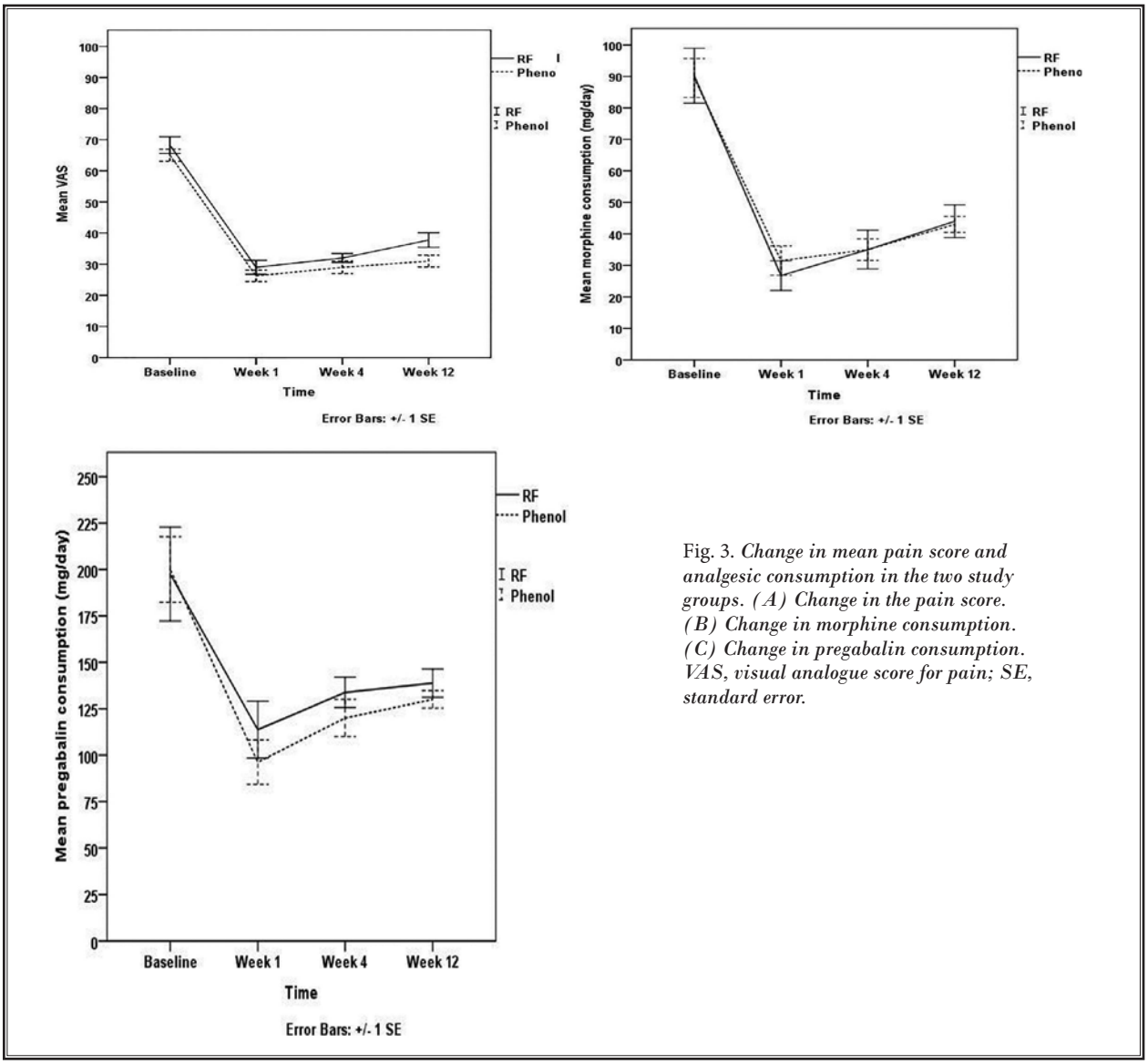

Fig. 3. *Change in mean pain score and analgesic consumption in the two study groups. (A) Change in the pain score. (B) Change in morphine consumption. (C) Change in pregabalin consumption. VAS, visual analogue score for pain; SE, standard error.*

Table 1. *Rating of self-reported functional improvement in the 2 study groups*

Time	Rating of functional improvement	RF (n = 20)	Phenol (n = 20)	*P*-value
Week 1	Marked (75% to 100) Moderate (50% to 75%) Mild (25% to 50%) Minimal (0 to 25%)	5 (25.0%) 7 (35.0%) 4(20.0%) 4(20.0%)	5 (25.0%) 8 (40.0%) 4 (20.0%) 3(15.0%)	.98
Week 4	Marked (75% to 100) Moderate (50% to 75%) Mild (25% to 50%) Minimal (0 to 25%)	5 (25.0%) 6 (30.0%) 5(25.0%) 4(20.0%)	4 (20.0%) 8 (40.0%) 5(25.0%) 3(15%)	.54
Week 12	Marked(75% to 100) Moderate (50% to 75%) Mild (25% to 50%) Minimal (0 to 25%)	4 (20.0%) 6 (30.0%) 6 (30.0%) 4(20.0%)	4 (20.0%) 7 (35.0%) 5(25%) 4(20%)	.98

Data are number (%)

Table 2. *Change in the Oswestry Disability Index ODI in the 2 study groups.*

Time	ODI	RF (n = 20)	Phenol (n = 20)	*P*-value
baseline	No disability	2 (10.0%)	2 (10.0%)	.470
	Mild disability	8 (40.0%)	11 (55.0%)	
	Moderate disability	8 (40.0%)	5 (25.0%)	
	Severe disability	1 (5.0%)	2 (10.0%)	
	Crippled	1 (5.0%)	0 (0.0%)	
Week 1	No disability	1 (5.0%)	1 (5.0%)	.545
	Mild disability	9 (45.0%)	12 (60.0%)	
	Moderate disability	9 (45.0%)	5 (25.0%)	
	Severe disability	0 (0.0%)	2 (10.0%)	
	Crippled	1 (5.0%)	0 (0.0%)	
Week 4	No disability	0(0%)	0(0%)	.828
	Mild disability	10 (50.0%)	8 (40.0%)	
	Moderate disability	8 (40.0%)	10 (50.0%)	
	Severe disability	1 (5.0%)	2 (10.0%)	
	Crippled	1 (5.0%)	0 (0.0%)	
Week 12	No disability	0(0%)	0(0%)	.490
	Mild disability	7 (35.0%)	4 (20.0%)	
	Moderate disability	11 (55.0%)	13 (65.0%)	
	Severe disability	1 (5.0%)	3 (15.0%)	
	Crippled	1 (5.0%)	0 (0.0%)	

Data are number (%)

the present study, selective thermal RF rhizotomy of S3 on 1 side combined with bilateral ablation of S4 and S5 was comparable to the conventional saddle rhizotomy with phenol regarding the control of pain and the functional improvement. The incidence of specific procedure-related adverse outcomes was also equivalent for both interventions, although per-patient incidence of major complications was significantly higher in the phenol group.

In recent years, there has been a growing trend toward deviation from the conventional analgesic ladder proposed by the WHO to the early administration of interventional procedures for managing cancer-related pain (18,19). The early application of pain blocks is believed to hamper central mechanisms involved in perpetuating the pain, thus reducing analgesic consumption and their related adverse effects, and improving the patient's quality of life. Moreover, this approach has the advantage of performing procedures before the anatomical landmarks are distorted by the growing tumor thus enhancing the success and reducing the complication associated with the intervention (20).

Table 3. *Incidence of adverse outcomes and complications in both study groups*

Adverse outcome / complication	RF (n = 20)	Phenol (n = 20)	*P*-value
Minor adverse events			
Back pain	4 (20%)	1 (5%)	.342
Post-dural puncture headache	0 (0%)	2 (10%)	.487
Aseptic meningitis	0 (0%)	1 (5%)	1.0
Hypotension	0 (0%)	1 (5%)	1.0
Major adverse events			
Dysthesia of lower limbs	0 (0%)	3 (15%)	.487
Lower limb paresis	0 (0%)	1 (5%)	1.0
Bladder dysfunction	0 (0%)	4 (20%)	1.0
Fecal incontinence	0 (0%)	2 (10%)	1.0
Per-patient incidence of major adverse events	0 (0%)	5 (25%)	.047

Data are number (%)

Several interventional modalities have been tried to control refractory perineal pain due to cancer. Although sympathectomy may be beneficial for pain of visceral origin, multiple pathways should be targeted to control peri-

Table 4. *Patients rating of satisfaction according to patent Global Impression of Changes (PGIC).*

SCORE	Patients Rating of Satisfaction	RF (n = 20)	Phenol (n = 20)	*P*-value
1	Very much improved	6 (30%)	6 (25.0%)	.847
2	Much improved	6(30%)	7(35%)	
3	Minimally improved	5(25%)	5(25%)	
4	No change	3(15%)	2(10%)	
5	Worse	0	0	
6	Much worse	0	0	
7	Very much worse	0	0	

neal pain associated with pelvic malignancies, including the superior and inferior hypogastric plexi as well as the ganglion impar. In contrast to the role of sympathetic blockade for pancreatic cancer, it has little evidence in pelvic malignancies (21). In addition, percutaneous cervical cordotomy (PCC) has little role in the treatment of midline perineal pain, should be performed bilaterally under CT guidance, and has considerable morbidity and mortality (22,23). Besides their potential for serious side effects, modalities such as intrathecal pumps and neuromodulation are expensive and require close surveillance with protracted after-care making their use impractical in developing countries (24-26).

To the authors' knowledge, this is the first RCT comparing thermal RF rhizotomy versus conventional chemical rhizotomy in patients with cancer-related perineal pain. We hypothesized that selective thermal RF rhizotomy could serve as a feasible alternative to conventional chemical saddle rhizotomy with fewer side effects. For decades, the latter has been in common use for patients suffering from intractable cancer-related perineal pain who have limited life expectancy. The procedure is relatively simple and inexpensive, can be performed repeatedly and requires little post-procedure care, rendering it suitable for areas with limited health care resources (27). It may be of reasonable efficacy regarding pain relief which has been reported to be in the order of a 50% -60% reduction that lasts for 3 to 6 months (12,28,29), despite the little evidence for such reports (9,11). However, a major concern for chemical rhizotomy is the potential for jeopardizing the neural control of the sphincters because of inadvertent spread of neurolytic agent to the anterior sacral roots involved in bladder and rectal control. In this regard, it has been suggested that unilateral preservation of S2 or S3 may preserve sphincteric function of both bladder and rectum (1,30), which is practically difficult to guarantee with chemical neurolysis owing to the unpredictable spread of neurolytic agents despite the usual precautions such as limiting the volume to the minimum effective dose, using hyperbaric solution or other precautions related to the patient's position during and after the procedure. In this context, thermal RF ablation has the assumed privilege of selectively delivering the intended lesioning to target roots while sparing others, thus minimizing the risk of sphincter dysfunction if performed in such way to salvage either of the S2 or S3 root on at least one side (1,30).

In the current study we used phenol rather than alcohol to avoid the burning dysesthesia and the possibility of vasospasm of the anterior segmental vessels associated with the latter agent (12). Besides, hyperbaric phenol in glycerin has the privilege of limited spread of injectate owing to its relatively high viscosity, while a concentration of 6% could help induce differential sensory blockade (9). We used a relatively wide-bore spinal needle (20-gauge) to minimize the jet-like spread of injectate. For the RF technique, we added lidocaine for its analgesic, vasodilator and neuroprotective effects and a steroid was injected before application of thermal lesioning to reduce the incidence of neuritis (31).

We reported sensory changes in the form of dysthesia of lower limbs in 3 cases. Two of them improved over 1 month, the third improved in 12 weeks. The patient who had motor paresis got better with time and physiotherapy after 12 weeks without permanent disability, 4 patients needed urinary catheterization: 1 patient recovered after 1 week, 2 patients needed the urinary catheter for a month and the fourth patient did not recover until the 12-week follow-up. Two patients developed fecal incontinence to nonformed stool, 1 of them improved in 3 weeks and the other continued till the 12 week follow up.

The overall incidence of major complications was significantly lower with the RF technique. While the incidence of specific adverse outcomes was not statisti-

cally significant, this could be due to the small sample size which is one of the limitations of this study. In view of the sparse evidence for the efficacy of conventional saddle rhizotomy (22) and the virtual lack of previous trials comparing both interventions, we based our power analysis on targeting a convenient effect size for the primary outcome measure that would be clinically relevant. We sought a rather large effect size (approximately a standardized difference of 1) which we deemed appropriate for the purpose of an exploratory study. The study may, on the other hand, have been under-powered regarding the adverse outcomes owing to the relatively small frequency of events that would require a much larger sample size to demonstrate statistical significance, if any, for a given difference, which may not be appropriate for a feasibility study. Another limitation is that the patients could not be blinded to the intervention they received owing to the technical uniqueness of either intervention. So, only the assessor was blinded (i.e., single-blinded trial) which could have been a possible source of bias.

Conclusion

To conclude selective thermal radiofrequency ablation of the S3 root on 1 side, S4 root on both sides and S5 roots could serve as feasible alternative to conventional saddle rhizotomy using hyperbaric phenol. Larger randomized controlled studies would be needed to confirm this finding and to demonstrate the assumed advatage of reducing adverse outcomes associated with dural tap especially impairment of sphincter control and possible neurological complications.

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