

Pre-operative diclofenac HPβCD for pain control of needle biopsy in musculoskeletal neoplasm: preliminary results

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Summary

Needle biopsy is the main standard method used for diagnosis of musculoskeletal tumors of the limbs and superficial trunk. Pain control during this procedure is through the use of Local Anaesthetic (L.A.). In order to achieve a complete pain control in our cases, recently we started using diclofenac HPβCD 50 mg via s.c. preoperatively. We present the clinical results of a non-randomized study of two heterogeneous groups of patients: "Experimental" Group (1): diclofenac HPβCD 50 mg via s.c. one hour before surgical procedure, local anesthesia and ev. diclofenac HPβCD 50 mg via s.c. 12 hours postoperative; "Conventional" Group (2): local anesthesia and ev. postoperative tramadol 100 mg via oral for pain control. In October 2014, at the Department of Orthopaedic Oncology and Reconstructive Surgery of Florence, 37 musculoskeletal biopsies for a bone or a soft tissue lesion were performed. Exclusion criteria for this study were: known allergies to lidocaine, diclofenac, tramadol; known gastric or duodenal ulcers; known gastrointestinal bleed or perforation; refusal of the patients to collaborate. For one or more of these reasons, 6 patients were excluded from this study. In the Group 1, 10 patients (59%) referred no pain during the surgical procedure (8/14 biopsies on soft tissue and 2/3 on bone). In 5 cases (29%) no exacerbation of previous chronic pain, and in 2 cases (12%) a progression of local pain after biopsy (av-

erage 1 points higher in the VAS). In Group 2, only 6 patients (42%) did not have any pain during the procedure, 4 (29%) no exacerbation of previous chronic pain and 4 (29%) a progression of local pain (average 2 points higher in the VAS). Despite similar results in both Groups, Group 1 seemed to have a mild better control of perioperative pain. The use of diclofenac HPβCD 50 mg preoperative seems to be a rational approach for minimizing perioperative pain and the preliminary data of our study seem encouraging. Obviously many bias are present in this study (small numbers of cases, heterogeneity of diseases, association with local anesthetic, non-randomized study, comparison between preoperative *versus* postoperative treatment) and this cannot absolutely be considered as definitive conclusions.

KEY WORDS: diclofenac HPβCD s.c.; pain control; needle biopsy musculoskeletal neoplasm.

Introduction

Needle biopsy is the main standard method used for diagnosis of musculoskeletal tumors of the limbs and superficial trunk.

Pain control during this procedure is through the use of Local Anaesthetic (LA). However, some patients still report pain during needle biopsy, ranging from mild discomfort to moderate pain.

While conventional drugs (diclofenac, tramadol, ibuprofen, nimesulide, etc.) are routinely employed for postoperative pain control, no preoperative drugs are utilized for a complete pain control in clinical practice.

Furthermore no scientific consensus have been published in musculoskeletal biopsies.

In order to achieve a complete pain control in our cases, recently we started using diclofenac HPβCD 50 mg via s.c. preoperative.

We present the clinical results of a non-randomized study of two heterogeneous groups of patients:

"Experimental" Group (1): diclofenac HPβCD 50 mg via s.c. one hour before surgical procedure, local anesthesia and ev. diclofenac HPβCD 50 mg via s.c. 12 hours postoperative;

"Conventional" Group (2): local anesthesia and ev. postoperative tramadol 100 mg via oral for pain control.

The purpose of the present study was to examine whether or not preoperative diclofenac HPβCD was effective in reducing the degree of intra-perioperative pain after a biopsy of musculoskeletal lesion, and which was the most efficacious association (1-5).

Material and methods

In October 2014, at the Department of Orthopaedic Oncology and Reconstructive Surgery of Florence, 37 musculoskeletal

Table 1 - Patients and type of pain control therapy.

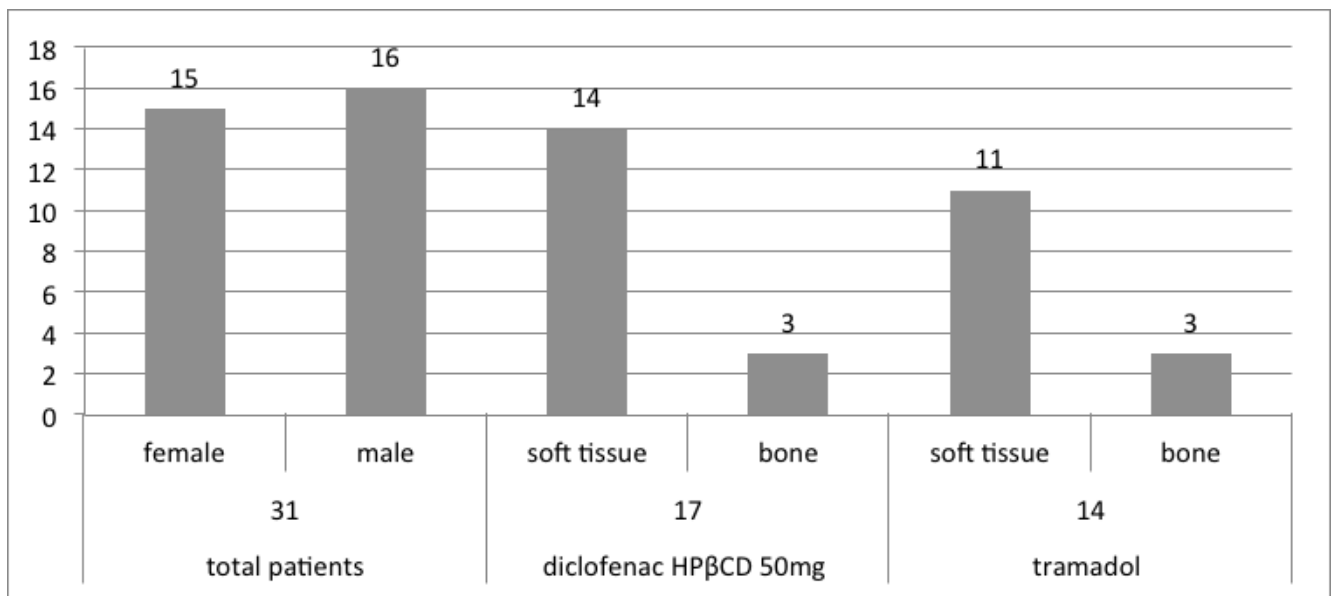
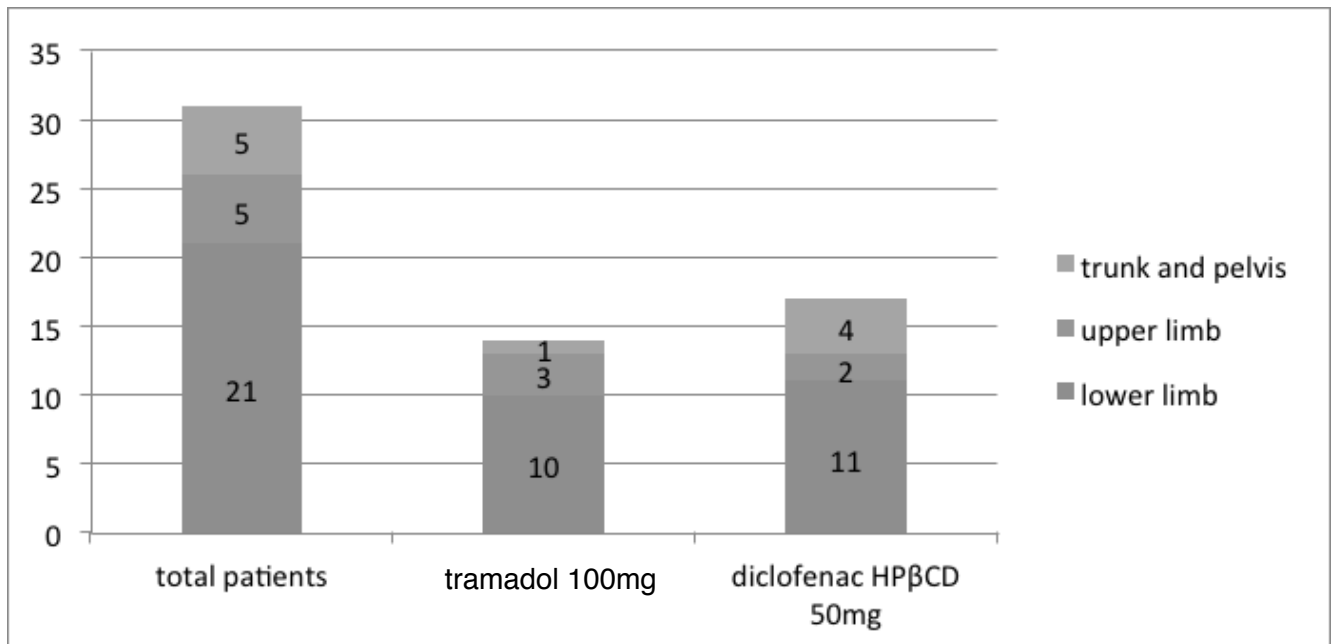


Table 2 - Site of biopsies.



biopsies for a bone or a soft tissue lesion were performed.

Exclusion criteria for this study were:

- known allergies to lidocaine, diclofenac, tramadol;
- known gastric or duodenal ulcers;
- known gastrointestinal bleed or perforation;
- refusal of the patients to collaborate.

For one or more of these reasons, 6 patients were excluded from this study.

Thirty-one enrolled patients gave fully informed consent for both the biopsy and their participation into the clinical trial.

17 cases (9 males and 8 females) received diclofenac HPβCD 50mg via s.c. preoperative (Group 1).

14 cases (7 males and 7 females) were suggested to use tramadol 100 mg tablet postoperative (Group 2) (Table 1).

In Group 1, diclofenac HPβCD 50 ml s.c. was injected one hour before biopsies in all cases, while in Group 2 no preoperative drugs were submitted.

Surgical procedure was the same in both groups: sterile dressing, injection through biopsy tract of 2% lidocaine (5/8 ml) and needle biopsies.

Regarding the site of biopsies, mostly interested soft tissues and lower limbs in both groups (Tables 1, 2).

After discharge, the patients of Group 1 were suggested to inject a new diclofenac HPβCD 50 ml s.c. 12 hours after the

Table 3 - Evaluation and side effects questionnaire.

NAME	<u>PAIN BEFORE BIOPSY</u> <u>(0 to 10)</u>
BIRTH DATE	<u>PAIN BEFORE DISCHARGE</u> <u>(0 to 10)</u>
TELEFON	<u>PAIN AT 20:00 (0 to 10)</u>
DIAGNOSIS (bone vs soft tissue)	<u>NIGHT PAIN (0 to 10)</u>
BODY AREA	<u>PAIN AFTER 24 H (0 to 10)</u>
ALLERGY (no NSADs , tramadolo, ibuprofen, nimesulide)	<u>COMPLICATIONS</u> <u>(hematoma, other)</u>
PREVIOUS USE OF PAINKILLERS (if so what and what effect)	<u>USE of Diclofenac HPβCD 50 mg</u> <u>(Yes or No)</u>
PRE-EXISTING CONDITIONS	<u>OTHER PAINKILLERS (Yes or No)</u>
ALREADY DONE SIMILAR PROCEDURES (Yes or No)	<u>HOW LONG AFTER BIOPSY</u> <u>PAINKILLERS TAKING (Hour and</u> <u>minutes)</u>
	<u>SUBJECTIVE DRUG EFFICACY</u> <u>(0 to 5)</u>

previous, in order to maximize the postoperative pain control; in Group 2 the patients were discharged with indication of tramadol 100, 1 tablet <after 6-8 hours, 3 time a days in case of persistent pain.

All patients were advised to call or return to our Centre if unexpected side effects occurred.

Two days after the biopsy, all patients received telephone follow-up by researchers, to obtain the clinical evolution and pain scores. Questions related to side effects experienced were also asked (Table 3).

Pain scores were recorded using the Visual Analog Scale (VAS) (6, 7) ranging from zero to 10, with zero corresponding to no pain or discomfort and 10 to maximal pain.

Pain scores was collected from all patients at these time-points:

- 1) before biopsy
- 2) pain/discomfort experienced during needle insertion
- 3) pain at biopsy
- 4) pain after 24 hours.

Pain scores were completed for all time-points by all patients included in the study.

Results

In the Group 1, 10 patients (59%) referred no pain during the surgical procedure (8/14 biopsies on soft tissue and 2/3 on bone), in 5 cases (29%) no exacerbation of previous chronic pain, and in 2 cases (12%) a progression of local pain after biopsy (average 1 points higher in the VAS).

One patients experienced a mild-moderate pain in the site of injection of diclofenac HPβCD 50 ml s.c., lasting one week after procedure.

At follow-up, 12/17 patients (71%) did not utilize any type of analgesic drugs. Only 5/17patients (29%) utilized the diclofenac HPβCD 50 ml s.c. for postoperative pain control. Average time of injection after biopsy was 26 hours (24-32),

with satisfactory results.

None of these 5 patients followed our suggestion to inject this drug 12 hours after surgery, suggesting that diclofenac HPβCD 50 ml s.c. preoperative achieved a longer time of pain relieve after surgery.

In Group 2, only 6 patients (42%) did not have any pain during the procedure, 4 (29%) no exacerbation of previous chronic pain and 4 (29%) a progression of local pain (average 2 points higher in the VAS).

Only 3/14 patients (21%) used tramadol 100mg, 1 tablet every 12 hours for two days, with acceptable pain control.

Comparing the overall results, needle biopsies of a musculoskeletal neoplasm seemed to be a well pain controlled procedures, with an average 50% of painless biopsies. Despite similar results in both Groups, Group 1 seemed to have a mild better control of perioperative pain (Table 4).

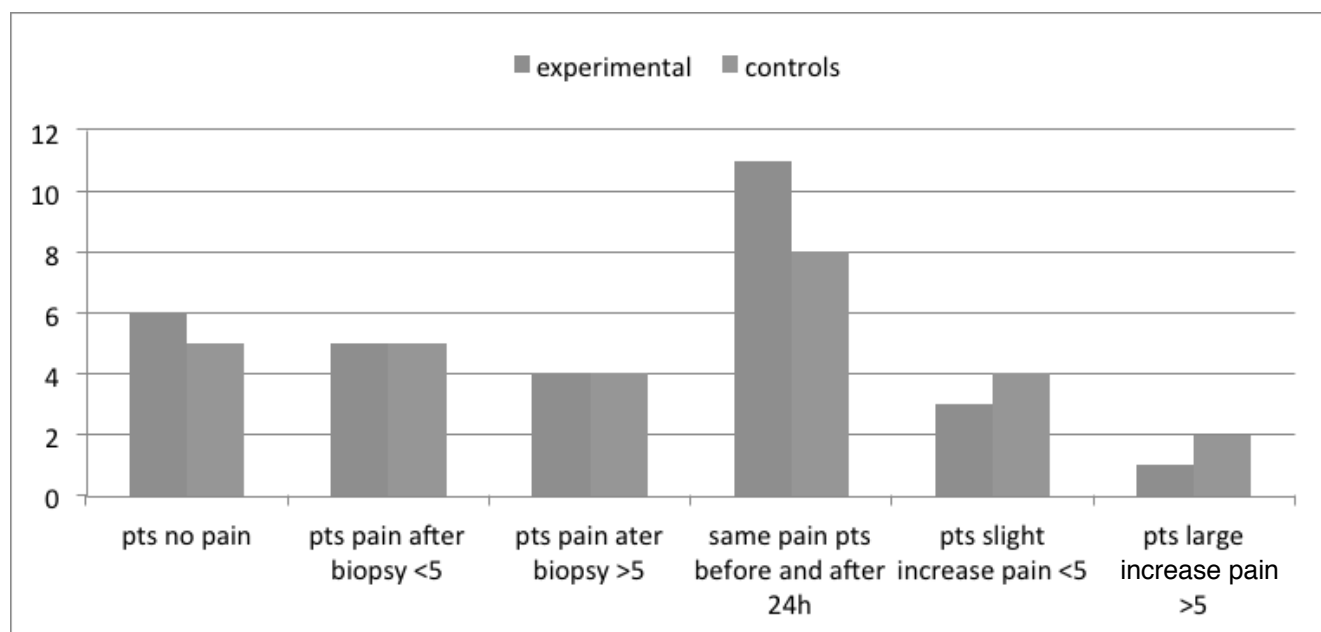
Discussion

Needle biopsies of musculoskeletal tumors of the limbs and superficial trunk is generally a well-tolerated procedure, mostly performed by local injection of anesthetic drugs. Although, some cases experienced a mild-acute pain perioperative and postoperative.

It is a well known consideration that even in apparently similar pain conditions, pain severity ratings and analgesic dosing requirements may differs considerably between individuals. This includes genetic and environmental origins, with epigenetic mechanisms and dynamic gene-environment interactions, more recently implicated in pain modulation. Indeed, more than 350 candidate pain genes have been identified as potentially contributing to heritable differences in pain sensitivity (8, 9).

Furthermore, age, gender, ethnicity, and actual level of stress, mood, or diseases may modify individual pain perception. This alters also the response to drug treatment, which represents a complex interaction between analgesic

Table 4 - Study's results of the two group.



medication and organism. Several mechanisms may be involved in the pain relief either as drug targets or as drug metabolizing enzymes/transporters, and the genetic variability in these processes influence the analgesic efficacy in individual patients (10).

It is worth remembering that inflammation is a recognized hallmark of cancer, that substantially contributes to the development and progression of malignancies, by complex interplay between local immune response (mediators of local inflammation, inflammasomes, presence of tumor necrosis, cytokines, transcription factors, chemokines, tumour immune-cell infiltrate) and systemic inflammation (mediator of systemic inflammation, acute-phase proteins, circulating immune-cell concentrations) which has great influence on clinical outcomes (11, 12).

Diclofenac belongs to the phenilacetic acid derivatives and is an anti-inflammatory, specifically inhibiting the enzyme cyclo-oxygenase that works locally and systematically (4). The primary mechanism responsible for its anti-inflammatory, antipyretic and analgesic action is inhibition of prostaglandins synthesis.

The use of diclofenac for the treatment of acute pain is widespread among physicians, both general practitioners and specialists, and Voltaren (Novartis Farma S.p.A. Origio (VA - ITA) is the most widely used of all by intramuscular injection (2).

The commercial introduction of diclofenac HP β CD (Akis - IBSA Farmaceutici Italia Srl, Lodi, ITA) allowed its use not only intramuscularly, but subcutaneously too, thanks to the increase of the solubility that allows an increased absorption in biological membranes and consequent greater speed of action and effectiveness; in addition, this formulation allowed the reduction of the volume to be injected from 3 ml to 1 ml.

Cyclodextrins are a family of compounds made up of six, seven or eight α -D-glucopyranoside units respectively called: α -cyclodextrin, β -cyclodextrin (less irritating and therefore more used) and γ -cyclodextrin. Cyclodextrins are relatively large molecules and act as carriers, maintaining hydrophobic the molecules of the drug in solution and transporting them

to the surface of biological membranes.

The dichlorophenyl-ring of the molecules is included in the cavities of HP β CD and, after injection, the complex rapidly dissociates releasing the active principle (5).

Regarding, instead, the subcutaneous administration site (abdomen, gluteal, quadriceps) a study performed by Salomone et al. in 2014 (4), showed no significant difference about both the bioavailability (AUC and Cmax are comparable for all three injection sites), and the rapidity of absorption (30 minutes) and the local tolerance. This suggests that this new formulation can be administered to any of these sites through the s.c. via without clinically significant differences.

Comparative studies have been performed (1) and they showed that the same results have been obtained with both doses of 50 mg and 75 mg, with greater safety and tolerability profile when the lower dose is used.

About the profile of the local tolerability, the result is comparable to that of Voltaren 75mg/3ml injected intramuscularly (3).

About the control group tramadol is a centrally acting analgesic which acts at opioid receptors and also appears to modify transmission of pain impulses by inhibition of monoamine reuptake. Tramadol has demonstrated analgesic activity in a number of animal models. In healthy volunteers with experimentally induced pain, oral tramadol exhibited analgesic activity similar to that of dextropropoxyphene and was more effective than flupirtine or dipyrrone (metamizole) but less effective than tilidine. The duration of analgesia with orally administered tramadol was 3 to 6 hours, with maximum pain relief reported at 1 to 4 hours post-dose. Intravenous tramadol 2 mg/kg was as effective as pethidine (meperidine) 1 mg/kg.

After oral administration as capsules or tablets, tramadol appears in the plasma within 15 to 45 minutes, reaching peak plasma concentrations at a mean of 2 hours. The absolute oral bio-availability of tramadol is approximately 68% after single doses and increases to 90 to 100% on multiple administration. Tramadol has a high tissue affinity with apparent volumes of distribution of 306 and 203L after oral and intravenous

administration, respectively, in healthy volunteers (13). Following all these considerations, pain perception and control appear to be extremely complex to deal with oncological cases.

Conclusions

Musculoskeletal biopsies are generally performed through local anesthesia. Literature reports suggest that, addition of anti-inflammatory drugs, can decrease pain experienced during and after biopsies.

The use of diclofenac HPβCD 50 mg preoperative seems to be a rational approach for minimizing perioperative pain and the preliminary data of our study seemed encouraging.

Obviously many bias are present in this study (small numbers of cases, heterogeneity of diseases, association with local anesthetic, non-randomized study, comparison between preoperative *versus* postoperative treatment) and this cannot absolutely be considerate as definitive conclusions.

The main “take home message” in clinical practice might be to routinely use an analgesic drug preoperative, possibly s.c. and long lasting, in order to minimize the discomfort and or peri-operative pain of a musculoskeletal biopsy.

A randomized and multicentric trial, with a larger amount of cases, is necessary to define which type of drugs are more painkillers in these procedures.

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