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Efficacy and tolerability of orally administered tramadol/dexketoprofen fixed- dose combination compared to diclofenac/thiocolchicoside in acute low back pain: experience from an Italian, single-centre, observational study

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Author contributions

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Abstract

Objectives: To compare the analgesic efficacy and tolerability of tramadol/dexketoprofen 75/25mg (TRAM/DKP) versus diclofenac/thiocolchicoside 75/4mg (DIC/THIO) in patients with moderate-to-severe acute low back pain (LBP).

Methods: Single-centre, observational study in 82 adult outpatients with LBP due to disc herniation (≥4 Numerical Rating scale, NRS) who received either oral TRAM/DKP (n=44) or intramuscular DIC/THIO (n=38), both given every 12 hours for 5 days. The primary endpoint was the change from baseline in pain intensity (PI) at pre-specified post-dose time points (t day1, t day3, t day7) and compared between the two treatments. Additional endpoints, all evaluated at day 7, included: the sum of PI difference (SPID), percentage of responders in terms of PI reduction versus baseline and change from baseline in Douleur Neuropathique (DN4) score. Tolerability and safety were also assessed.

Results: Both treatment groups were comparable for demographic characteristics and comorbidities. Over the 5-day treatment period and up to day 7, compared to DIC/THIO, TRAM/DKP provided a significantly greater and sustained analgesia at day 3 and day 7 ($p<0.0001$), with a higher proportion of responders at each time point [75 % versus 71.1 % ($p = 0.687$) at day 1, 93.2% versus 73.7% at day 3 ($p=0.016$) and 95.5% versus 71.1% at day 7 ($p=0.003$)], higher values of SPID (770.9 ±23.5 *vs.* 507.1 ±22.6; $p<0.0001$) and significantly greater reduction in DN4 score [-62.7±25.6 *vs.* -39.7±31.2 ($p<0.0001$)]. Both treatments were well tolerated.

Conclusions: Orally administered TRAM/DKP 75/25 mg can be a valuable and effective option in patients with acute LBP.

Keywords: low back pain; dexketoprofen; tramadol; NSAIDs; muscle relaxant

Short title: Tramadol/dexketoprofen is effective in acute low back pain

Introduction

Low back pain (LBP) is an extremely common and disabling condition, with nearly 80-90% of adults experiencing it at least once in their lifetime [1,2], and stands as top primary and urgent care complaint worldwide [3]. LBP is now the leading cause of disability globally and poses substantial burden on both healthcare systems and society as a whole, that is projected to increase even further in coming decades in terms of sick leave, lost workdays, years lived with disability and early retirement [4]. To date, the economic impact related to LBP has been estimated being comparable to other prevalent and costly conditions including cardiovascular disease, cancer, mental health and autoimmune diseases [4,5].

Among the wide range of spinal conditions leading to LBP, lumbar disc herniation (LDH) is one of the most common spinal degenerative disorders leading to LBP associated with radiculopathy [6]. Inflammatory response has been acknowledged to be important in the process of disc degeneration thus playing an important role in pain generation; as a result, lumbar disc herniation (LDH) is highly associated with inflammation in the context of low back pain [7]. Nevertheless, radiculopathy is mostly of neuropathic origin [8] and it has been estimated that 80% of patients with neurological signs corresponding to typical radiculopathy display pain with neuropathic component [9]. The large majority of these patients (about 90% to 95%) will respond to conservative treatment [10] that is characterized by a lower risk of complications than surgery and is preferred by the vast majority of patients; of note, surgery did not show a benefit over conservative treatment in midterm and long-term follow-up [11].

Although most episodes of LBP are short-lasting and may resolve even in absence of treatment, LBP is increasingly understood as a long-lasting condition with a variable course and a high risk of recurrence and chronicity [4,12]. A mounting evidence suggests that despite most episodes of acute LBP may improve substantially within weeks, two-thirds of patients still report some pain at three months and one-third will have a recurrence within one year of recovering from a previous episode thus becoming prone to develop chronic LBP [2,13-15]. Given the complex interplay of both nociceptive and neuropathic components underlying chronic LBP pathophysiology and the untidy pattern of pain trajectories observed in the most severe patients, chronic LBP management is far from being optimal and requires early intervention in patients with acute LBP in order to prevent progression to chronic LBP [16].

Despite the large variety of both pharmacological and non-pharmacological interventions currently available, discrepancies in LBP management among health professionals' practices and variation among guidelines with regard to recommendations for pain relief make selecting the most appropriate medication for LBP patients a great challenge [17,18]. For treatment of patients with acute LBP, some guidelines recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids for short periods [5] while other advice the use of NSAIDs or skeletal muscle relaxants [2] thus leaving uncertainty on which analgesic intervention may provide optimal pain relief during the acute phase of LBP. Of note, current guidelines [2,5] either advise against the use of paracetamol or indicated no difference in effectiveness between paracetamol and placebo thus not considering it as a valid option in patients with LBP. LBP is generally treated in an outpatient setting with NSAIDs being either delivered by intramuscular (IM) or oral route. Despite the common belief of IM being preferable to oral route, no conclusive data support this assumption; in contrast, IM mode of administration is frequently associated with several drawbacks including bruising, potential for hematoma formation and needle-stick injury [19,20].

Owing to its pharmacological profile, the oral fixed dose combination tramadol/dexketoprofen 75/25mg (TRAM/DKP) may provide pain control in acute exacerbations of LBP and be suitable for mixed types of pain including non-specific LBP where nociceptive and neuropathic mechanisms are involved at both local and central levels [21]. While some evidence on the clinical efficacy of TRAM/DKP in acute LBP had been reported [22], further evaluation is needed. Diclofenac/thiocolchicoside 75/4mg (DIC/THIO) is an intramuscular (i.m.) fixed-dose combination of a NSAID and a muscle-relaxant that has shown an analgesic efficacy greater than that achieved by its monocomponents in patients with moderate-to-severe acute LBP [23]. The present study was designed to compare the analgesic efficacy and tolerability of TRAM/DKP *vs.*

DIC/THIO in patients with moderate-to-severe acute LBP, namely, lumbar radiculopathy due to disc herniation during a 5-day treatment period.

Methods

Study setting and design

This was a single-centre, retrospective, observational study including two treatment arms (TRAM/DKP and DIC/THIO) and conducted in 82 patients (42 women, 40 men) treated at our clinic (Valle Giulia, Rome, Italy) between September 2017 and March 2018. Participation in the study lasted approximately 1 week for each patient and was made up of four study visits: baseline (t0), at the first 24 h (day 1) and 72 h (day 3) and at the end of the 5-day treatment period (day 7). Visits at the investigational study site were performed at approximately the same time of the day. At baseline, patients rated pain intensity (PI) using an 11-numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain). The present investigation consists of a retrospective analysis and we have collected data from patients who, experiencing moderate to severe pain (≥4), were treated with either tramadol/dexketoprofen 75/25 mg (TRAM/DKP) (Dextradol®, Malesci) *per os* or diclofenac 75mg (Voltaren®, Novartis) + thiocolchicoside 4mg i.m. (Muscoril®, Sanofi) (DIC/THIO) every 12 hours for 5 days. The choice of therapy was often based on patient preferences for either oral or intramuscular route of administration. Patients' preferences were highly valued during pain therapy prescription as advocated by international guidelines recommending that clinicians and patients should use a shared decision-making approach to select the most appropriate treatment based on patient preferences, availability, harms, and costs of the intervention [2]. Furthermore, patients who might less tolerate injections could be better suited to receive oral tablets and *viceversa*. Rescue medication (paracetamol 1000 mg, with a maximum recommended daily dose of 3 g) was allowed during the entire treatment period. study protocol (CVG07012020) was approved by the reference Ethic Committee of the investigational study site prior to study start. Patients gave their written informed consent during the baseline study visit.

Patients

In order to be eligible to participate, patients met all of the following criteria: 1) Adult aged between 18 and 80 years; 2) diagnosis of lumbar disc herniation as assessed by magnetic resonance imaging; 2) Acute radicular pain with onset no more than 7 days prior to the screening visit and moderate to severe intensity [(≥4 on 11-point NRS)]. The following conditions did not permit participation in the study: known allergy or hypersensitivity to study treatments, active cervical/dorsal disc herniation, active or suspected aesophageal, gastric, pyloric channel or duodenal ulceration or bleeding in the last 30 days, uncontrolled blood pressure, use for more than 7 days of analgesics (different from study medication like weak opioids or acetaminophen or other NSAIDs such as ketorolac, nimesulide, naproxen, ibuprofen, indometacin or ketoprofen) in the weeks before the study. Moreover, patients with 18.5> BMI<35 were not enrolled as well as patients unable to sign the consent agreement were excluded. Lastly, use of other analgesics, drugs acting on pain perception (e.g. opioids, psychotropic agents, anti H1 agents or analgesics like gluco-corticosteroids, NSAIDs) or anticoagulants (e.g. heparinoids, warfarin) were not permitted.

Efficacy evaluation

The primary efficacy endpoint was the change from baseline in pain intensity measured at rest during the 5-day treatment period at pre-specified post-dose time points (t day1, t day3, t day7). Pain intensity was recorded using the NRS scale (0="no pain", 1-3="mild pain", 4-6="moderate pain", 7-9="severe pain", 10="worst possible pain"). Secondary endpoints included the sum of pain intensity difference (SPID) at the study end (day 7), percentage of responders in terms of PI reduction, namely subjects who achieved at least 30% of PI reduction at day 7 *vs.* baseline and change from baseline in Douleur Neuropathique (DN4) score at day 7. To distinguish between the presence and absence of neuropathic pain, the Italian version of the clinician-administered questionnaire DN4 was used (scores ≥4/10 being considered indicative of neuropathic pain) [24,25].

Safety evaluation

The safety evaluation was based on the incidence, seriousness, intensity and causal relationship of spontaneously reported treatment-emergent adverse events (TEAEs), *i.e*. AEs occurred after the first study drug administration. AEs were assessed throughout the entire study by means of a non-leading open question. Spontaneously reported AEs and early discontinuation of therapy were also recorded (only by patients' feedback, no BP or other parameters were registered).

Statistical analysis:

Descriptive statistics were used to summarize the characteristics of study participants. Categorical variables were reported as frequencies (percentages) and continuous variables as mean (SD). The association between categorical variables was tested by the Pearson Chi-Square test or Fisher's Exact test, when appropriate. Student's t-test was used to compare mean values in terms of SPID, DN4 score at the end of treatment period (day 7). A one-way repeated-measures analysis ANOVA was used to assess differences in PI change score over time. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were carried out using SPSS software (SPSS version 21, SPSS Inc., Chicago, IL, USA).

Results

Patient population

Overall, 82 patients were enrolled with 44 receiving TRAM/DKP *per os* and 38 DIC/THIO via i.m. The mean age of the patients was 57.6 (9.7) years, with a balanced gender distribution (40 males and 42 females). Demography and baseline clinical characteristics were comparable between TRAM/DKP and DIC/THIO treatment groups and are summarized in Table 1. In both treatment groups, the majority of patients presented a lumbar disc herniation mostly localized to L4-L5 (54.5% *vs.* 52.6%) and L5-S1 (25% *vs.* 26.3%) in TRAM/DKP and DIC/THIO respectively (p=0.99; data not shown). With respect to LBP risk factors and associated comorbidities (namely smoking status, hypertension, diabetes and overweight), there were no differences between groups with a limited proportion of patients being current smoker (18.2% *vs.* 21%), hypertensive (25% *vs.* 15.8%) and diabetic (6.8% *vs.* 10.5%) in TRAM/DKP and DIC/THIO, respectively. Of note, the mean BMI indicated that few of them were obese (n=8 and n=7 in TRAM/DKP and DUC(THIO group, respectively). Patients reported mean (SD) NRS-PI values at baseline of 8.8 (0.75) and 8.7 (0.75) in the TRAM/DKP and DIC/THIO group, respectively. About 70% of patients experienced severe pain (NRS-PI > 8) prior study drug administration (72.7% and 68.4% in TRAM/DKP and DIC/THIO treatment groups, respectively; p=0.746). Finally, there were no differences between treatment groups in DN4 patient score at baseline (6.0 *vs.* 5.8; p=0.686). Overall, the study population comprised patients who were not only suffering from severe acute LBP but also experiencing neuropathic pain.

Efficacy results

Primary endpoint

The course of pain severity over the treatment period is presented in Figure 1. Overall, the mean pain intensity progressively decreased from baseline over the 5-day treatment period and up to day 7 only in patients receiving TRAM/DKP with a significantly greater and sustained analgesia at day 3 and day7 (p<0.0001) compared to those being treated with DIC/THIO. Of note, the analgesic efficacy of DIC/THIO remained unchanged over time with no further improvement after the first day of treatment (Figure 1).

Secondary endpoints

Over the 5-day treatment period, higher percentages of responders (patients achieving at least 30% of PI reduction) were observed for TRAM/DKP than for DIC/THIO [75 % *vs.* 71.1 % (p = 0.687) at day 1, 93.2% *vs.* 73.7% at day 3 (p=0.016) and 95.5% *vs.* 71.1% at day 7 (p=0.003)] (Figure 2 and Table 2). At day 7, among responders, significantly higher proportion of patients experienced PI reduction greater than 50% following treatment with the TRAM/DKP than with DIC/THIO (63.6% *vs*. 5.3%, p<0.0001) (Figure 3). Accordingly, the PI analysis at day 7 indicated higher values of SPID for TRAM/DKP than with DIC/THIO group (770.9±23.5 *vs.* 507.1±22.6; p<0.0001). In addition, as the enrolled patients suffered from a neuropathic component, we evaluated whether changes from baseline at the end of the treatment period (day 7) could be observed: patients receiving TRAM/DKP experienced a significantly greater reduction in DN4 score from baseline (-

62.7±25.6) compared to those treated with DIC/THIO (-39.7±31.2) (p<0.0001). Finally, there were no statistically significant differences in the consumption of rescue medication (RM) between treatment groups with none of enrolled patients taking RM more than five times during the entire treatment period (data not shown).

Safety and tolerability

Overall, both treatments were tolerated with 8 (18.2%) and 3 (7.9%) patients experiencing TEAE in the TRAM/DKP and DIC/THIO group, respectively. No serious adverse events were reported and none of patients in the two groups discontinued the therapy due to TEAEs. Furthermore, no epileptic seizure event was reported in the DIC/THIO group as patients with known hypersensitivity to THIO were excluded from the study. The treatment-related TEAE in the DIC/THIO group consisted of pain in the site of injection (7.9%). The treatment-related TEAE in the TRAM/DKP group consisted of somnolence (9.1%) and constipation (9.1%) observed during the study period from day 1 to day 7, 55% recorded at day1, 35 % recorded at day 3, 10% at day 7, registered during the period (phone calls or clinical examinations). These percentages are in line with the tolerability profile documented in over 2,500 patients in both Phase II and III trials with TRAM/DKP and reported in Smpc [26].

Discussion

LBP management poses substantial challenges to physicians, due to its natural course and high risk of recurrence and chronicity. Thus, effective and adequate pain control in the acute phase of LBP may help preventing chronicity; however, no clear consensus has been reached on the optimal therapeutic approach for acute LBP. While international guidelines recommend the use of NSAIDs and weak opioids [5] or muscle relaxants [2], there is also a rising increase in the use of anticonvulsants in clinical practice as alternative to opioids despite their limited evidence-based efficacy in LBP [27]. Previous comparative studies supported the use of the investigated combinations in the management of moderate to severe acute pain. The fixed-dose combination TRAM/DKP has shown greater analgesic efficacy than mono-components alone in well-established human models of acute visceral and somatic moderate to severe pain [28-30] and sustained greater analgesia and a more rapid onset of action when compared to tramadol/acetaminophen combination in a dental pain model [31]. Similarly, combining diclofenac with thiocolchicoside has shown an analgesic efficacy greater than that achieved by its mono-components in patients with moderate-to-severe acute LBP [23] and in orthopedic patients [32] while being less effective than diclofenac/eperisone in LBP patients [33]. To improve appropriateness of pharmacotherapy in clinical practice, head-to-head comparisons may provide valuable evidence as well as guidance for use of analgesics in highly prevalent and challenging conditions such as LBP.

Our study provides first clinical evidence of the analgesic efficacy of the fixed-dose combination TRAM/DKP in patients with LBP due to lumbar radiculopathy when compared to a recently developed fixed-dose combination DIC/THIO.

The 5-day treatment with TRAM/DKP was effective at progressively reducing PI as early as 24h post first dose with significantly greater pain reduction at day 3 and day 7 compared to DIC/THIO (p<0.0001). The time course of PI reduction shows the ability of TRAM/DKP to confer a sustained analgesia thus resulting in almost the majority of patients (95.5%) achieving at least 30% of PI reduction by day 7. Of note, the high percentage of patients achieving 30% reduction of pain intensity prompted us to deepen this information from a qualitative standpoint, only for explorative purpose, by assessing proportion of patients experiencing an even higher PI reduction up to 50%. Interestingly, two third of patients receiving TRAM/DKP experienced more than 50% reduction in PI compared to about 5% of those being treated with DIC/THIO thus further supporting the greater analgesic efficacy of TRAM/DKP. Overall, the pain reduction by 50% stands as an additional piece of information that it might be useful to better discriminate the differences between the two treatment groups.

From a clinical standpoint, our findings expand current knowledge on subtle differences existing between DKP and DIC. An earlier study showed that a 2-day treatment with intramuscular DKP 50 mg twice-daily

was equally effective to DIC 75 mg twice-daily in severe acute LBP with lower proportion of patients in DKP group experiencing AEs compared to those in DIC group [34]. A more recent retrospective study comparing DKP and DIC in patients undergoing 6-week treatment for chronic pain of the lumbosacral spine revealed lower values of PI on the disability index in patients receiving DKP and significant changes in the dynamics of PI [35]. Interestingly, the analysis of correlation between PI and degree of disability demonstrated a higher correlation between these two parameters in DKP-receiving patients thus suggesting that the administration of DKP may result in a more rapid restoration of full physical activity [35]. Overall, previous findings seem to support the notion that, once pain is better managed, physical therapy and physicians-guided exercises are widely recommended following acute episodes of LBP and may become more feasible for patients to return to an active lifestyle. In addition to symptomatic pain relief, facilitating early return to normal activities is a goal of NSAIDs therapy; thus, the choice of NSAID appears fundamental in determining the effectiveness of the analgesic therapy. In this regard, it is clinically relevant that almost one third of patients receiving DIC/THIO did not even achieve at least the 30% reduction of PI by day 7 thus potentially becoming prone to experience a recurrence. In line with our observations, a previous study assessing the analgesic efficacy of DIC/THIO in LBP patients reported that up to 20% of them used paracetamol as rescue medication for pain relief thus partially undermining the analgesic potential of this fixed-dose combination [23]. Accordingly, earlier evidence by Perna et al. in non-specific LBP suggested that consistently greater proportion of patients receiving DIC/THIO required rescue medication compared to those receiving TRAM/DKP from day 1 (77.7% *vs.* 26.2%) to day 4 (46.6% *vs.* 11.9%) of the study period [22].

Our study presents some similarities with that by Perna et al. However, compared to the study population of Perna et al that included patients with non-specific LBP, our 'focused' inclusion (MRI confirmed lumbar disc herniation) is of additional value as well as the assessment of analgesic efficacy over time at very short time interval that allowed us to depict the patient response and detect relevant differences in the onset of pain relief. Overall, our study complements and expands the earlier evidence reported by Perna et al. thus further consolidating the clinical evidence supporting the use of TRAM/DKP combination in such clinical setting.

It has been documented that 20% of patients with LBP pain suffer from a NP component [36] whose presence is associated with more severe pain symptoms and higher healthcare utilization costs [16]. Thus, strategies effectively targeting both nociceptive and neuropathic components are highly desirable. In our study, we provide first preliminary evidence that TRAM/DKP is effective at reducing DN4 score at greater (up to 1.5-fold) extent compared to DIC/THIO. This finding may be suggestive of a potential use of TRAM/DKP for targeting neuropathic component in LBP with tramadol mostly contributing to the observed effect by virtue of its centrally-acting mechanism of action and documented efficacy in *in vivo* models of neuropathic pain [37]. Although future larger studies are needed to confirm and expand our preliminary observations, our data suggest that TRAM/DKP may hold a great potential as a valuable alternative to anticonvulsants that are increasingly prescribed by physicians seeking medications devoid of addition risk despite their limited evidence-based efficacy in radicular pain and the increased risk for adverse events [27].

We acknowledge that our study suffers from some limitations. First, this is a convenience sample of patients seen in a single centre in Italy and may not be generalizable to other populations where patterns of treatment and care may vary. Second, the study design as prospective investigation may not exclude a risk of selection bias. Third, our study did not include a placebo arm thus potential placebo-derived effect contributing to PI reduction could not be ruled out. Fourth, whether the greater analgesic efficacy of TRAM/DKP vs. DIC/THIO would translate in improved mobility and physical function was not investigated.

In conclusion, our study provides first evidence that oral TRAM/DKP 75/25 mg can be a valuable and effective option in patients with acute LBP due to lumbar disc herniation. Considering that the optimal management of acute and recurrent LBPs has not yet been established, our findings could pave the way to larger randomised studies with the final aim of expanding the clinical use of TRAM/DKP 75/25 mg in LBP.

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Table 1. Patient demographic and baseline characteristics by treatment group.

Demographic and baseline characteristics	TRAM/DKP N=44	DIC/THIO N=38	*P value*
Age (years) Mean (SD)	57.7 (10.4)	57.6 (9.2)	*0.071*
Sex (n, %) Female Male	 21 (47.7) 23 (52.3)	 21(55.3) 17(44.7)	*0.500*
Smoking status (>5 cigarettes/day) (n,%) YES NO	 8 (18.2) 36 (81.8)	 8 (21) 30 (79)	*0.699*
Hypertension (n,%) YES NO	 11 (25) 33 (75)	 6 (15.8) 32 (84.2)	*0.305*
Diabetes (n,%) YES NO	 3 (6.8) 41 (93.2)	 4 (10.5) 34 (89.5)	*0.549*
Body mass index Mean (SD)	26.2 (3.3)	27.6 (2.9)	*0.091*
Baseline Pain intensity (NRS-PI) Mean (SD) 6≤NRS-PI≤8 (n, %) NRS-PI> 8 (n, %)	 8.8 (0.75) 12 (27.3) 32 (72.7)	 8.7 (0.75) 12 (31.6) 26 (68.4)	*0.746*
Baseline DNIV Mean (SD)	6.0 (1.9)	5.8 (1.9)	*0.686*

DIC, diclofenac 75mg; DKP, dexketoprofen 25mg; DNIV, douleur neuropathique index value; NRS-PI, numerical rating scale-pain intensity; SD, standard deviation; THIO, thiocolchicoside 4mg; TRAM, tramadol 75mg.

Table 2. Proportion of patients achieving ≥ 30% NRS-PI reduction at day 7.

Reduction NRS-PI score ≥ 30	TRAM/DKP (N=44) N (%)	DIC/THIO (N=38) N (%)	**P value**
YES	42 (95.5)	27 (71.1)	0.003
NO	2 (4.5)	11 (28.9)	

DIC, diclofenac 75mg; DKP, dexketoprofen 25mg; NRS-PI, numerical rating scale-pain intensity; SD, standard deviation; THIO, thiocolchicoside 4mg; TRAM, tramadol 75mg.

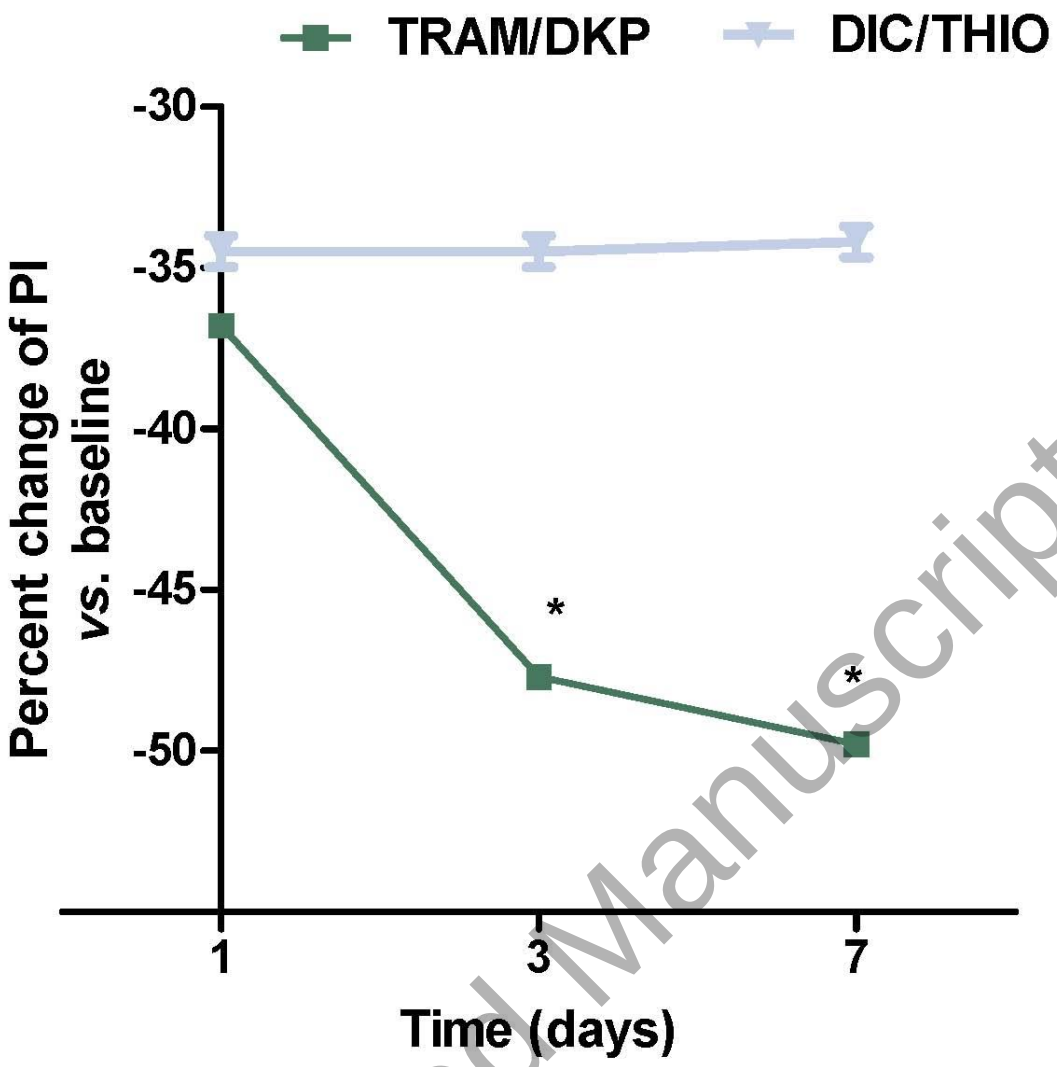

Figure 1. Analgesic efficacy over time. *Statistically significant TRAM/DKP *vs.* DIC/THIO (p<0.0001). PI, pain intensity; DIC/THIO, diclofenac/thiocolchicoside 75/4mg; TRAM/DKP, tramadol/dexketoprofen 75/25mg

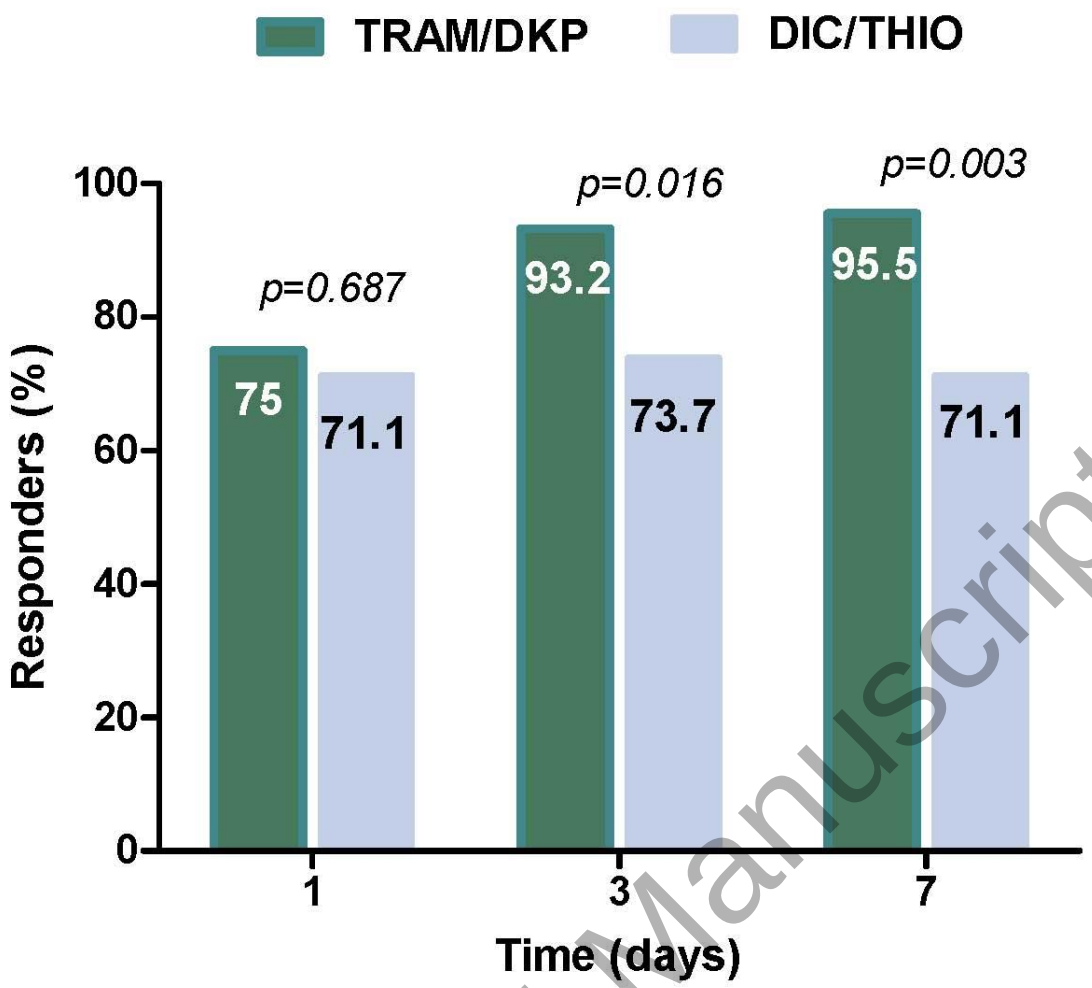

Figure 2. Percentage of responder patient by treatment and time points. Response defined as at least 30% PI reduction. Statistically significant difference between TRAM/DKP and DIC/THIO at day 3 and day 7 (p=0.016 and p=0.003, respectively). PI, pain intensity; DIC/THIO, diclofenac/thiocolchicoside 75/4mg; TRAM/DKP, tramadol/dexketoprofen 75/25mg.

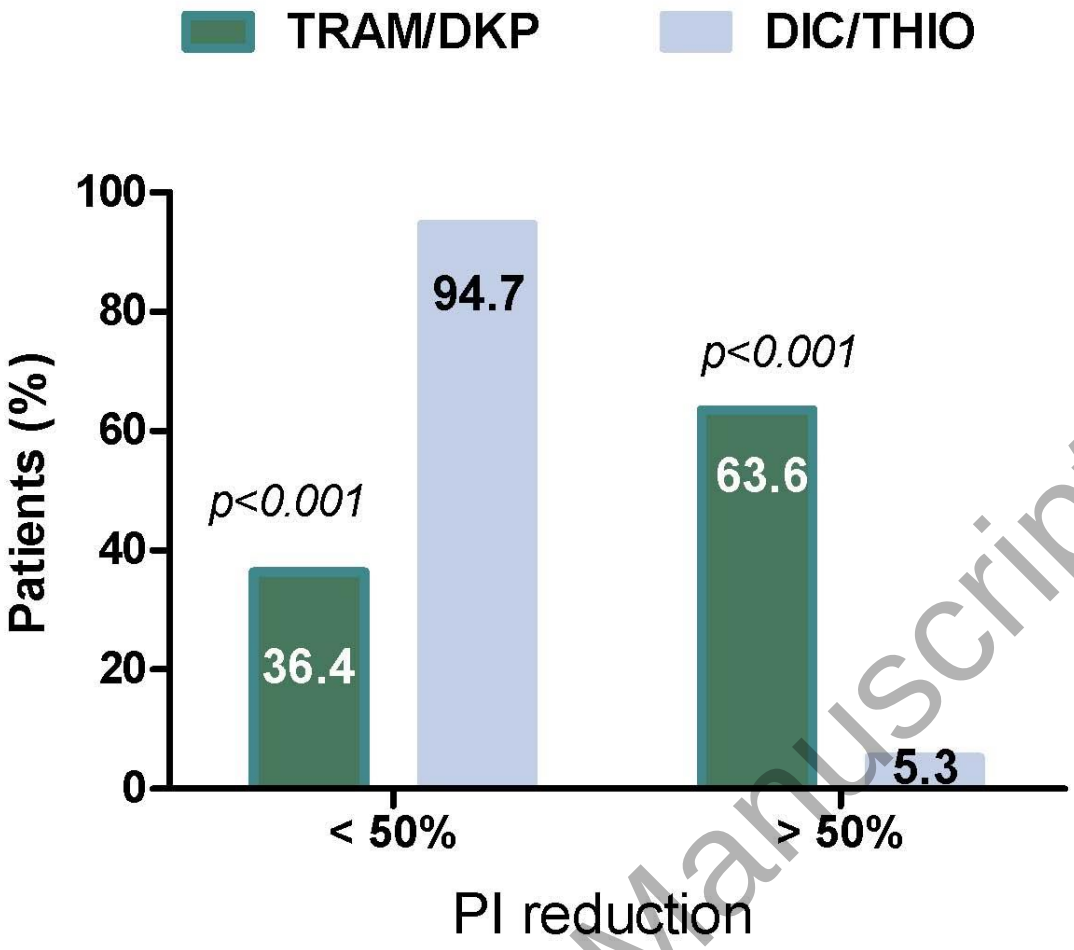

Figure 3. Proportion of patients achieving PI reduction at day 7 by defining response as at least 50% PI reduction. Statistically significant difference between TRAM/DKP and DIC/THIO (p<0.001). PI, pain intensity; DIC/THIO, diclofenac/thiocolchicoside 75/4mg; TRAM/DKP, tramadol/dexketoprofen 75/25mg.