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GORECKI, P. <<http://orcid.org/0000-0002-5657-5001>>, RAINSFORD, Kim, TANEJA, P., BULSARA, Y., PEARSON, D., SAUND, D., AHMED, B. and DIETRICH, T. <<http://orcid.org/0000-0002-2557-7645>>

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Submucosal Diclofenac for Acute Postoperative Pain in Third Molar Surgery: A randomized, controlled clinical trial

¹ Patricia Gorecki, Dr. med. dent, ² Kim D. Rainsford, PhD, ¹ Pankaj Taneja, ¹ Yogesh
Bulsara, ¹ David Pearson, ¹ Daniel Saund, ¹ Bilal Ahmed, ¹ Thomas Dietrich, Dr. med.
dent.

¹ The School of Dentistry, Institute of Clinical Sciences, University of Birmingham,
Birmingham Dental Hospital Edgbaston, B5 7EG, UK

² Biomedical Research Centre, Sheffield Hallam University, Sheffield, S1 1WB, UK

Address for Correspondence:

Professor Thomas Dietrich,
The School of Dentistry,
Birmingham Dental Hospital,
Institute of Clinical Sciences,
University of Birmingham,
5 Mill Pool Way,
Edgbaston, Birmingham, B5 7EG, England, UK
Tel: 0044-1214665495
Email: t.dietrich@bham.ac.uk

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Abstract

Diclofenac sodium is a widely used non-steroidal anti-inflammatory drug (NSAID) for relief of inflammatory pain. A recent formulation combines this drug with hydroxypropyl- β -cyclodextrin (HP β CD) to improve its solubility and to enable subcutaneous administration. Previous studies confirmed the efficacy of this combination. This study's aim was to evaluate the efficacy, safety and local tolerability of diclofenac HP β CD administered as a local submucosal injection prior to lower third molar surgery. We conducted a prospective, randomised, double-blind, placebo-controlled, parallel-group phase II single centre study. Seventy-five patients requiring mandibular third molar surgery were randomised into one of five groups: 5mg/1mL diclofenac HP β CD, 12.5mg/1mL diclofenac HP β CD, 25mg/1mL diclofenac HP β CD, 50mg/1mL diclofenac HP β CD or 1mL placebo. The respective study drug was injected into the mucosal tissue surrounding the surgical site prior to surgery following achievement of local anaesthesia. The primary outcome measure was the Area Under the Curve (AUC) of cumulative pain scores over the time from end of surgery to 6 hours post-surgery. This demonstrated a global treatment effect between the active groups and placebo, hence confirming the study drug's efficacy ($p=0.0126$). Secondary outcome measures included the time until onset of pain and the time until patients required rescue medication, both showing statistical significance of the study drug compared to placebo ($p<0.0161$ and $p<0.0001$, respectively). The time until rescue medication ranged between 7.8hrs (for 25mg/1mL diclofenac HP β CD) and 16hrs (for 50mg/1mL diclofenac HP β CD). Interestingly, the 5mg/1mL solution appeared superior to the 12.5mg/1mL and 25mg/1mL (time until rescue medication = 12.44hrs). A total of 14% of patients experienced minor Adverse Drug Reactions (ADRs) of which two cases demonstrated flap necrosis. These

resolved without further intervention. The study results overall indicate efficacy, safety and relative tolerability of diclofenac HP β CD used locally as a submucosal injection prior to third molar surgery (ClinicalTrials.gov-Identifier: NCT01706588).

Introduction

Diclofenac is a well-established non-selective non-steroidal anti-inflammatory drug (NSAID). Due to its anti-inflammatory, anti-pyretic and analgesic properties it is commonly used to treat acute/chronic pain, and inflammation (Barden et al. 2004; Blair and Plosker 2015; Gan 2010; Hersh et al. 2004; Moore 2007; Moore et al. 2015c; Sengupta et al. 1985). Diclofenac sodium's acidic form is poorly soluble (Sengupta et al. 1985) and therefore available as the sodium salt with pharmaceutically acceptable solvents, e.g. propylene glycol and benzyl alcohol to enable intramuscular (IM) and intravenous administration. Recent formulations use the complexing agent hydroxypropyl- β -cyclodextrin (HP β CD), serving as a solubility enhancer and facilitating smaller volumes for subcutaneous (SC) or submucosal application (Albers and Muller 1995; Blair and Plosker 2015), with previous studies confirming its successful and safe SC use (Chiarello et al. 2015; Dietrich et al. 2014; Zeitlinger et al. 2012).

Local submucosal drug injection is well-established with local anaesthetics, but otherwise rarely used. The submucosal injection of dexamethasone (Chen et al. 2017; Moraschini et al. 2016; Saravanan et al. 2016) in the context of lower third molar (LM3) surgery is a notable exception. Submucosal injection of analgesics has been described with ketorolac in endodontic pain management (Penniston and Hargreaves 1996) and tramadol in LM3 surgery (Cecchetti et al. 2014), combining the advantages of parenteral drug administration with an administration route that every dentist will be comfortable with. Both studies evaluated standard analgesic doses of the respective analgesic drug.

However, we hypothesized that local submucosal injection of diclofenac may achieve analgesia at markedly lower than standard analgesic doses, taking advantage of high

concentrations locally at the site of tissue insult. This would be an attractive novel concept, potentially achieving analgesia while minimising side-effects. We planned the present study to meet two objectives; (i) to provide proof-of-principle or otherwise of low dose local analgesia and (ii) to evaluate the potential for submucosal diclofenac HP β CD as a pre-emptive analgesic in LM3 surgery, as this would have immediate clinical application, if effective. The aim of the present study was therefore to investigate the efficacy, local tolerability and safety of pre-emptive submucosal injection of different diclofenac HP β CD doses for postoperative analgesia in a phase-II, proof-of-principle study.

Materials and Methods

Study design

This investigator-initiated trial was a prospective, randomised, double-blind, placebo-controlled, parallel-group, phase-II single-centre study, conducted at The School of Dentistry, University of Birmingham and the Birmingham Dental Hospital, Birmingham, UK. Ethical approval was obtained by the Ethics Committee, Office for Research Ethics Committees Northern Ireland. The trial adhered to the Declaration of Helsinki and the International Conference on Harmonisation (ICH) consolidated Guideline on Good Clinical Practice (GCP).

Patients (aged 18 to 65), referred for the surgical removal of a LM3 under local anaesthesia (LA) requiring osteotomy, were eligible to participate (please see online appendix for full list of inclusion/exclusion criteria). Written informed consent had to be provided to be enrolled.

Intervention

Patients received one of four diclofenac HP β CD (Akis®/Dicloin®, IBSA, Lugano, Switzerland) doses (50mg/1mL, 25mg/1mL, 12.5mg/1mL or 5mg/1mL), or 1ml placebo (sterile water, Appendix Figure 1).

Randomisation, allocation concealment and blinding

The investigational drug and preparation instructions were supplied packed in identical, sealed boxes, numbered sequentially according to a pre-defined, computer-generated randomisation list in blocks of 10 (i.e., with two kits for each treatment dose level). No stratification was used. None of the investigators were aware of the randomisation method for the duration of the study to minimise risk of selection bias.

Following confirmation of all eligibility criteria on the surgery day, the next available randomisation number was allocated to the patient. A single trained study-team member (PT), not involved in any other study procedure, opened the corresponding study medication pack and prepared the syringe for injection in a separate room. Placebo, 25mg and 50mg ampoules appeared identical; however, 5mg and 12.5mg formulations were prepared by diluting a 25mg ampoule with water for injection, with relevant instructions being contained in the medication pack. All 1mL syringes were delivered unmarked to the surgeon for administration. Neither the surgeon nor any other study-team member was made aware of its contents.

Surgery and follow-up

Experienced Oral Surgeons performed the LM3 removal within 30 days of the screening visit using a standard surgical protocol (see Appendix). The study medication was injected in three sites buccal to the LM3 (approximately equal distance apart, about 0.33mL per site), following achievement of LA.

During the postoperative 6-hour-observational period at the investigational site pain measurements (using a 0-100mm Visual Analogue Scale (VAS)), the amount of rescue medication (RM) consumed (i.e. 500mg paracetamol tablets) and surgical site appearance regarding bleeding, local irritancy/tolerability were recorded. Patients were then discharged and continued to make hourly pain ratings and recorded any RM intake in a postoperative diary for a further 6 hours. From the day after surgery, patients recorded the RM amount and an overall pain rating for each postoperative day (using a 0-100mm VAS) on a daily basis for one week.

Patients returned for two follow-up visits (=day 2 and 7 post-surgery) to assess postoperative extra-oral swelling, trismus and wound healing and verify RM consumption.

Where required, extractions of any additional teeth were performed outside the trial.

Baseline/Surgical Data

A number of demographic, lifestyle and surgical data were collected at the respective study visits (see Appendix).

Outcome measures and statistical analyses

The primary endpoint was the Area Under the Curve (AUC) of pain scores over time (assessed using 0-100mm VAS), from end of surgery until 6 hours post-surgery compared between treatment groups.

Assuming a standard deviation of 20mm and a mean difference (over the 6 hours) between groups of 25mm, a sample size of 12 patients per group would be required for two-by-two comparisons at $\alpha=0.05$ and 80% power. Therefore, 15 patients per group were considered sufficient to preliminarily investigate the treatment's efficacy.

The following secondary endpoints were evaluated (see Appendix for further details):

- AUC of pain scores over the 12-hour-observation period post-surgery
- Time to onset of pain and time to RM
- Extra-oral swelling and trismus 6 hours post-surgery, on day 2 and 7
- Peak-Pain-Intensity and RM consumption
- Cumulative proportions of patients using RM over the 6-hour-in-clinic-observation period

- Adverse events

Prespecified analysis plan

Baseline/surgical characteristics were summarised by treatment group to evaluate whether the groups were balanced at randomisation, with mean/standard deviation used for continuous measures and number/percentage for categorical variables.

Baseline characteristics were compared between the study groups using ANOVA models and Fisher's exact test.

Missing VAS pain scores or values after RM for the timed assessments in the 12h-postoperative period were replaced by using a linear interpolation method. For this purpose, the linear trend between the last two valid VAS scores was used to replace the missing value. Patients' pain ratings on postoperative days were not replaced, irrespective of timing of RM intake.

Three populations were considered for analysis, Intention-To-Treat (ITT), Per-Protocol (PP) and Safety Population (see Appendix for details).

The primary endpoint analysis was conducted using both ITT and PP. Additionally to the unadjusted analyses, a multivariable analysis was performed, adjusting for BMI, amount of bone removal and gender in the ANOVA model. Post-hoc testing for pairwise comparisons between active and placebo groups did not adjust for multiple comparisons.

All other endpoints were analysed using the ITT principle. Safety variables (AEs) were assessed using the Safety Population.

Treatment effect estimates were reported with 95% confidence intervals and statistical tests performed at $\alpha=0.05$.

Results

We screened 80 patients between January and May 2013. Out of the 75 randomised patients, 15 each were allocated to the 5mg, 12.5mg and 25mg diclofenac HP β CD group, 14 to the 50mg HP β CD group and 16 to placebo (Appendix Figure 1).

Protocol violations

Two patients were excluded from the PP population due to major protocol violations, i.e. missing or delayed (=delay \geq 15mins from scheduled time) pain measurements, which occurred in the 6-hour post-surgery period.

Demographic/surgical characteristics

Demographic and surgical characteristics were overall well-balanced between study groups (Table 1).

Efficacy variables

Primary outcome measure

We found a global treatment effect in both ITT and PP populations ($p=0.0126$ and $p=0.0057$, respectively). In contrast, no statistically significant differences were found between the active study arms (Table 2, Figure 1).

Adjustment for sex, BMI and amount of bone removal as covariates, also confirmed a global treatment effect between active and placebo arms ($p=0.0188$). Likewise, no statistically significant difference was noted between the diclofenac groups. Also, none of the covariates exerted an influence on the primary variable.

Secondary outcome measures

The AUC of VAS scores over the 12-hour postoperative period revealed similar results to the 6-hour postoperative period with the Least Square Means (LSMs) being lower in the active groups compared with placebo ($p=0.0471$). A global treatment effect was seen between the diclofenac groups and placebo apart from the comparison between 25mg diclofenac HP β CD and placebo ($p=0.1093$). No statistically significant differences were observed between active treatment groups (Table 2, Figure 1).

The active groups exhibited longer time until pain onset compared to placebo ($p=0.0161$ for overall treatment effect). Again, no statistical differences were found between diclofenac groups (Table 2, Figure 2).

The time until first RM was significantly shorter in the placebo group compared to the active treatment groups, demonstrating again a global treatment effect ($p<0.0001$). Between the active groups no statistically significant differences were observed (Table 2, Figure 3).

The cumulative proportion of patients taking RM over the 6-hour-period post-surgery was higher in placebo compared with the diclofenac groups ($p=0.0483$) (Table 2).

Peak-Pain-Intensity analysis showed no global treatment effect ($p=0.8595$). Likewise, evaluation of trismus revealed no statistically significant differences between active groups and placebo, measured at 6 hours ($p=0.1691$), 2 days ($p=0.5428$) and 7 days ($p=0.6260$) post-surgery. Similar findings were observed for the extra-oral swelling measured at 6 hours ($p=0.3855$) and 2 days ($p=0.5933$). However, a global treatment effect was noted at 7 days after surgery, with a small but statistically significant difference in favour of the diclofenac groups compared to placebo ($p=0.0214$) (Table 2).

Safety/tolerability

AEs and Adverse Drug Reactions (ADRs=AEs occurring after injection of study drug and with causal relationship to study drug, as judged by investigator) were monitored throughout the study period. The causal relationship between AEs and the study drug was assessed at the time when the event occurred.

The number of patients experiencing at least one AE was 8 (=53.3%) in the 5mg Diclofenac group, 9 (=60%) in the 12.5mg, 8 (=53.3%) in the 25mg and 5 (=35.7%) in the 50mg group. Six (=37.5%) AEs were reported amongst placebo patients (Appendix Table 1). The number of participants experiencing AEs did not differ significantly between groups. The most frequently occurring AEs were headache, vomiting and facial swelling (Appendix Table 2).

The percentage of ADRs was 13.3% in both the 5mg and 12.5mg Diclofenac group, 33.3% in the 25mg and 14.3% in the 50mg group. Placebo group patients did not report any ADRs (Appendix Table 1). The most frequent ADRs were injection site reactions, i.e.pain or swelling (Appendix Table 3). Two cases of flap necrosis were observed during the post-operative observation period. One mild ulceration arose in the 25mg group at the 2-day review appointment and one moderate ulceration was observed in the 50mg group at the 7-day review appointment (Appendix Figure 2 and 3). These resolved spontaneously, without requiring any countermeasures. The number of ADRs did not differ significantly between groups.

No Serious Adverse Events (SAEs) were recorded.

Discussion

This trial aimed at evaluating the safety, tolerability and efficacy of varying doses of diclofenac HP β CD (5mg, 12.5mg, 25mg, 50mg) injected locally prior to LM3 surgery.

The choice of diclofenac sodium as an anti-inflammatory analgesic for relief of mild-moderate dental pain is supported by (a)extensive studies reported from the Cochrane database (Barden et al. 2004; Moore 2007; Moore et al. 2015b; Moore et al. 2015c) showing this drug's effectiveness in dental pain with low AE incidence encountered with other NSAIDs and analgesics (Gan 2010; Moore et al. 2015a); (b)rapid absorption from oral/parenteral preparations and other favourable pharmacokinetic properties (Sengupta et al. 1985) as well as its ability to accumulate into the cerebrospinal fluid and pain inhibition in the central nervous system (Bjorkman and Elam 1993; Kokki et al. 2008); and (c)its novel mechanism of analgesia involving selective effects on ion channels (Duan et al. 2012; Gwanyanya et al. 2012) quite separate from its well-known actions as a potent inhibitor of cyclo-oxygenases and inflammatory-pain-producing prostaglandins (Gan 2010; Rainsford 2015), lipoxygenases (Gan 2010), nitric oxide-cGMP anti-nociceptive pathway activation and NMDA-receptor analgesia (Gan 2010). Some of these actions delineate diclofenac from other NSAIDs and may contribute to its potent effects as an acute pain-relieving drug.

All four drug dose levels produced significantly superior effects compared with placebo in preventing pain during the 6-hour post-surgical observation period in terms of pain intensity levels, time until pain onset and time to first RM intake. The results are consistent with findings from previous studies showing the efficacy of the

parenterally administered sodium diclofenac HP β CD formulation (Blair and Plosker 2015; Chiarello et al. 2015; Dietrich et al. 2014).

No dose-dependent effects were observed in the four active groups in any of the evaluated endpoints. The lack of dose-dependency could be related to zero-order kinetics that may be apparent with the localised intra-mucosal delivery of high concentrations of the drugs. Zero-order kinetics have been observed with several drugs administered subcutaneously, including those from controlled-release systems (Cho et al. 1982; Hill et al. 2012; Liu et al. 2007; Mei et al. 2010). Interestingly, the 5mg dose demonstrated slightly better analgesic efficacy over the 6- and 12-hour postoperative evaluation period, although this was not significantly different from that observed with the other dose levels. Also, the time until pain onset and RM was longer than in the 12.5mg and 25mg group. The concept of locally/sub-mucosally injected analgesics is a fairly unexplored territory. The local pharmacokinetic profile of submucosal diclofenac HP β CD is not known. Comparing the pharmacodynamic responses involving pain relief in the present and previous studies (Dietrich et al. 2014) with pharmacokinetic data is only possible in relation to the SC administration route of HP β CD diclofenac into the thigh. Thus, previous studies have shown essentially bioequivalence of 75mg/mL of this formulation when given SC with that when given IM and similar to that with diclofenac sodium as Voltaren® given IM (Zeitlinger et al. 2012). The drug is rapidly absorbed with peak concentrations being achieved from SC and IM administration of HP β CD diclofenac at about 1hr, while those from IM diclofenac sodium were evident at 0.45hr suggesting that the HP β CD may act as a moderate slow-release system. The peak diclofenac concentrations from HP β CD diclofenac are slightly higher following IM compared with both SC administered drugs (Zeitlinger et al. 2012). Overall, however, both formulations

achieve similar absorption when administered as the sodium salt or the HP β CD formulation. The volumes of distribution, median residence time and elimination half-life are comparable among the formulations and suggest that the drug is rapidly distributed and eliminated from both formulations. Therefore, an alternative explanation may be that in the context of the dental pain impaction model, a low dose of 5mg is as efficacious as the higher doses. However, topically applied solutions (e.g. Voltaren®) demonstrate a 10x delayed maximal plasma concentration (Altman et al. 2015), and if submucosal application showed a similarly delayed effect the here observed findings could be explained in this way. Furthermore, the vasoconstrictor in the LA, administered immediately before the submucosal diclofenac injection, may also have resulted in a delay of systemic distribution of the drug. Hence, the analgesic effects of submucosal diclofenac observed in the present study could be attributable to local or systemic drug effects, or a combination of both.

We found no evidence for submucosal HP β CD diclofenac injection to have meaningful efficacy as a pre-emptive analgesic (i.e., having analgesic efficacy beyond 5.5 half-lives), as there were no clinically important differences in terms of analgesic consumption or pain levels over the postoperative week (data not shown).

We evaluated the submucosal HP β CD diclofenac's efficacy in a modified (pre-emptive) dental pain impaction model for several reasons. Firstly, we were interested in evaluating an approach that would be suitable for use in clinical practice, as LM3 surgery is usually provided as an outpatient procedure and patients would not be able to inject themselves intra-orally postoperatively. Secondly, previous studies have shown that SC injections may cause some pain/discomfort, which would be minimised with a pre-emptive approach as it allowed submucosal injection following LA.

The main reported ADRs were injection site reactions, i.e. pain or swelling, reported in 14.6% of active group patients, which concurs with previous evaluations (Blair and Plosker 2015; Dietrich et al. 2014); although this was somewhat surprising given that the injection was given following LA. Previous studies have shown that there were no serious adverse reactions following SC administration of sodium diclofenac HP β CD at three dose levels of 25, 50 and 75mg/mL (Dietrich et al. 2014; Zeitlinger et al. 2012). Furthermore, Salomone et al. (Salomone et al. 2014) have shown that there are few subjects that showed local reactions to 50mg sodium diclofenac HP β CD at the injection sites in the abdomen, gluteus and quadriceps muscles, with all local reactions being mild-moderate and disappearing by 10mins (i.e. hardening) or 30mins (i.e. swelling and redness).

In the present study, a flap necrosis was observed in two subjects, one in the 25mg and one in the 50mg group (Appendix Figures 2/3). These were highly unusual and not observed previously by the investigators in LM3 surgery. Both resolved without further interventions and without any sequelae. Among the rare adverse skin reactions that have been reported being associated with parenteral injection of diclofenac (Dadaci et al. 2015; Kilic et al. 2014; Nischal et al. 2009) and other drugs (Seremet et al. 2015), antibiotics (Alkan Bozkaya et al. 2016) and vaccines (Rygnestad and Kvam 1995; Stefano et al. 2017; Wronecki and Czernik 1981) is the Nicolau syndrome (Livedoid dermatitis or *Embolia cutis medicamentosa*). This was first reported in 1924 by Freudenthal (James et al. 2015; Kilic et al. 2014; Nischal et al. 2009) and is a rare iatrogenic condition characterised by an immediate erythematous skin reaction following injection or ischaemic reaction (pallor) sometimes with a reticular pattern leading to necrosis of the skin and underlying tissue which can be severe and lead to disfigured scarring (James et al. 2015). We believe that the two occurrences of flap

necrosis could be unusual mucosal manifestations of Nicolau syndrome. Although previous reports on Nicolau syndrome have implicated diclofenac itself, we cannot rule out HP β CD as a possible cause.

The results of the present study have to be cautiously interpreted due to the limited sample size of this phase-II study, which unsurprisingly resulted in some chance imbalances between groups in terms of patient and surgical characteristics. Thus, confounding by these and other unmeasured factors has to be considered.

Overall, this study indicates efficacy, safety and relative tolerability of diclofenac HP β CD as a local submucosal analgesic. The study provides evidence in support of the novel concept of low-dose local analgesia for the first time. Further studies should include investigation of the study drug's local pharmacokinetics, and larger phase-III trials are required to confirm efficacy and safety of low-dose submucosal analgesia for acute pain management.

Authors' contributions

TD designed research. TD, PT, YB, DP, DS and BA conducted research. PG, KR and

TD wrote the paper. TD had primary responsibility for final content.

All authors read and approved the final manuscript.

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References

- Albers E, Muller BW. 1995. Cyclodextrin derivatives in pharmaceuticals. *Crit Rev Ther Drug Carrier Syst.* 12(4):311-337.
- Alkan Bozkaya T, Demirel G, Ormeci T, Al S, Cakar E, Tastekin A, Turkoglu H. 2016. Anticoagulant and vasodilator therapy for nicolau syndrome following intramuscular benzathine penicillin injection in a 4 year old boy. *Arch Argent Pediatr.* 114(3):e184-186.
- Altman R, Bosch B, Brune K, Patrignani P, Young C. 2015. Advances in nsaid development: Evolution of diclofenac products using pharmaceutical technology. *Drugs.* 75(8):859-877.
- Barden J, Edwards J, Moore RA, McQuay HJ. 2004. Single dose oral diclofenac for postoperative pain. *Cochrane Database Syst Rev.* (2):CD004768.
- Bjorkman R, Elam M. 1993. Diclofenac evaluated in a human experimental model of central pain. *Pain.* 54(2):197-202.
- Blair HA, Plosker GL. 2015. Diclofenac sodium injection (akis((r)), dicloin ((r))): A review of its use in the management of pain. *Clin Drug Investig.* 35(6):397-404.
- Cecchetti MM, Negrato GV, Peres MP, Deboni MC, Naclerio-Homem Mda G. 2014. Analgesic and adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 117(3):e249-254.
- Chen Q, Chen J, Hu B, Feng G, Song J. 2017. Submucosal injection of dexamethasone reduces postoperative discomfort after third-molar extraction: A systematic review and meta-analysis. *J Am Dent Assoc.* 148(2):81-91.
- Chiarello E, Bernasconi S, Gugliotta B, Giannini S. 2015. Subcutaneous injection of diclofenac for the treatment of pain following minor orthopedic surgery (direct study): A randomized trial. *Pain Pract.* 15(1):31-39.
- Cho MJ, Kurtz RR, Lewis C, Machkovech SM, Houser DJ. 1982. Metronidazole phosphate--a water-soluble prodrug for parenteral solutions of metronidazole. *J Pharm Sci.* 71(4):410-414.
- Dadaci M, Altuntas Z, Ince B, Bilgen F, Tufekci O, Poyraz N. 2015. Nicolau syndrome after intramuscular injection of non-steroidal anti-inflammatory drugs (nsaid). *Bosn J Basic Med Sci.* 15(1):57-60.
- Dietrich T, Leeson R, Gugliotta B, Petersen B. 2014. Efficacy and safety of low dose subcutaneous diclofenac in the management of acute pain: A randomized double-blind trial. *Pain Pract.* 14(4):315-323.
- Duan KZ, Xu Q, Zhang XM, Zhao ZQ, Mei YA, Zhang YQ. 2012. Targeting a-type k(+) channels in primary sensory neurons for bone cancer pain in a rat model. *Pain.* 153(3):562-574.
- Gan TJ. 2010. Diclofenac: An update on its mechanism of action and safety profile. *Curr Med Res Opin.* 26(7):1715-1731.
- Gwanyanya A, Macianskiene R, Mubagwa K. 2012. Insights into the effects of diclofenac and other non-steroidal anti-inflammatory agents on ion channels. *J Pharm Pharmacol.* 64(10):1359-1375.

- Hersh EV, Levin LM, Adamson D, Christensen S, Kiersch TA, Noveck R, Watson G, 2nd, Lyon JA. 2004. Dose-ranging analgesic study of prosorb diclofenac potassium in postsurgical dental pain. *Clin Ther.* 26(8):1215-1227.
- Hill A, Geissler S, Weigandt M, Mader K. 2012. Controlled delivery of nanosuspensions from osmotic pumps: Zero order and non-zero order kinetics. *J Control Release.* 158(3):403-412.
- James WD, Berger TG, Elston DM. 2015. Andrew's diseases of the skin. Clinical dermatology. WB Saunders.
- Kilic I, Kaya F, Ozdemir AT, Demirel T, Celik I. 2014. Nicolau syndrome due to diclofenac sodium (voltaren(r)) injection: A case report. *J Med Case Rep.* 8:404.
- Kokki H, Kumpulainen E, Laisalmi M, Savolainen J, Rautio J, Lehtonen M. 2008. Diclofenac readily penetrates the cerebrospinal fluid in children. *Br J Clin Pharmacol.* 65(6):879-884.
- Liu Y, Lu WL, Wang JC, Zhang X, Zhang H, Wang XQ, Zhou TY, Zhang Q. 2007. Controlled delivery of recombinant hirudin based on thermo-sensitive pluronic f127 hydrogel for subcutaneous administration: In vitro and in vivo characterization. *J Control Release.* 117(3):387-395.
- Mei L, Bao J, Tang L, Zhang C, Wang H, Sun L, Ma G, Huang L, Yang J, Zhang L et al. 2010. A novel mifepristone-loaded implant for long-term treatment of endometriosis: In vitro and in vivo studies. *Eur J Pharm Sci.* 39(5):421-427.
- Moore N. 2007. Diclofenac potassium 12.5mg tablets for mild to moderate pain and fever: A review of its pharmacology, clinical efficacy and safety. *Clin Drug Investig.* 27(3):163-195.
- Moore RA, Derry S, Aldington D, Wiffen PJ. 2015a. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of cochrane reviews. *Cochrane Database Syst Rev.* (10):CD011407.
- Moore RA, Derry S, Aldington D, Wiffen PJ. 2015b. Single dose oral analgesics for acute postoperative pain in adults - an overview of cochrane reviews. *Cochrane Database Syst Rev.* (9):CD008659.
- Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L. 2015c. Non-prescription (otc) oral analgesics for acute pain - an overview of cochrane reviews. *Cochrane Database Syst Rev.* (11):CD010794.
- Moraschini V, Hidalgo R, Porto Barboza E. 2016. Effect of submucosal injection of dexamethasone after third molar surgery: A meta-analysis of randomized controlled trials. *Int J Oral Maxillofac Surg.* 45(2):232-240.
- Nischal K, Basavaraj H, Swaroop M, Agrawal D, Sathyanarayana B, Umashankar N. 2009. Nicolau syndrome: An iatrogenic cutaneous necrosis. *J Cutan Aesthet Surg.* 2(2):92-95.
- Penniston SG, Hargreaves KM. 1996. Evaluation of periapical injection of ketorolac for management of endodontic pain. *J Endod.* 22(2):55-59.
- Rainsford K. 2015. Pharmacology and toxicology of ibuprofen. In: Rainsford K, editor. *Ibuprofen: Discovery, development and therapeutics.* Wiley-Blackwell. p. 132-236.
- Rygnestad T, Kvam AM. 1995. Streptococcal myositis and tissue necrosis with intramuscular administration of diclofenac (voltaren). *Acta Anaesthesiol Scand.* 39(8):1128-1130.

- Salomone S, Piazza C, Vitale DC, Cardi F, Gugliotta B, Drago F. 2014. Pharmacokinetics of a new subcutaneous diclofenac formulation administered to three body sites: Quadriceps, gluteus, and abdomen. *Int J Clin Pharmacol Ther.* 52(2):129-134.
- Saravanan K, Kannan R, John RR, Nantha Kumar C. 2016. A single pre operative dose of sub mucosal dexamethasone is effective in improving post operative quality of life in the surgical management of impacted third molars: A comparative randomised prospective study. *J Maxillofac Oral Surg.* 15(1):67-71.
- Sengupta C, Aféche P, Meyer-Brunot HG, Rensing U. 1985. Diclofenac sodium. In: Rainsford K, editor. *Anti-inflammatory and anti-rheumatic drugs volume ii: Newer anti-inflammatory drugs.* CRC Press. p. 49-63.
- Seremet S, Turan E, Erdemir AT. 2015. Nicolau syndrome following intramuscular injection of oxytocin in pregnant women: Report of two cases. *Dermatol Online J.* 21(8).
- Stefano PC, Garello M, Nolte MF, Lamy P, Giglio N, Castellano V, Gentile A. 2017. [nicolau syndrome induced by intramuscular injection of a hexavalent vaccine in a 6-month-old girl]. *Arch Argent Pediatr.* 115(1):e13-e16.
- Wronecki K, Czernik J. 1981. [the nicolau syndrome in children (author's transl)]. *Z Kinderchir.* 32(4):367-370.
- Zeitlinger M, Rusca A, Oraha AZ, Gugliotta B, Muller M, Ducharme MP. 2012. Pharmacokinetics of a new diclofenac sodium formulation developed for subcutaneous and intramuscular administration. *Int J Clin Pharmacol Ther.* 50(6):383-390.

Figure legends

Figure 1 – Pain intensity over time

Pain intensity of the respective study groups from end of surgery until 12 hours post-surgery

VAS = Visual Analogue Scale

Figure 2 – Time to pain onset

Kaplan Meier survival curve demonstrating the time until onset of pain following surgery in the respective study groups

Figure 3 – Time to first rescue medication

Kaplan Meier survival curve illustrating the time until the first rescue medication was consumed postoperatively in the respective study groups