Submucosal diclofenac for acute postoperative pain in third molar surgery: A randomized, controlled clinical trial

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

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Appendix / Supplemental Material

Study design

Females of childbearing potential were required to have a negative urine pregnancy test at the inclusion visit and be using an appropriate contraception method throughout the study period. The following exclusion criteria applied:

- Patients refusing to give written informed consent or to return for control visits
- Patients enrolled in a clinical trial in the previous 3 months
- Pregnant or breast-feeding women
- Patients with an allergy to diclofenac/other NSAIDs
- Patients on medication that could affect the efficacy and/or safety outcomes assessed in this trial, e.g. corticosteroids, other NSAIDs, anticoagulant/antiplatelet agents or antimicrobials.
- Patients with a history of gastrointestinal disorders, coagulation disorders, hepatic/renal/cardiac impairment, peripheral arterial disease or uncontrolled hypertension
- Patients with major psychiatric disorders compromising study participation in the investigator's opinion
- Alcohol or drug abuse in the previous 12 months

Surgery and follow-up

Patients received an appointment for their LM3 removal within 30 days of their screening visit. Lidocaine 2% with 1:80.000 epinephrine (Septodont, Maidstone, Kent, UK) was used for LA (administered as an inferior dental nerve block and buccal infiltration). The maximum allowed dose of 8.8mL included intraoperative supplemental administration, if necessary. Once LA was achieved a 1mL submucosal injection of the study medication was given in three sites (approximately equal distance apart) buccal to the third molar area, with about 0.33mL given per site.

Experienced oral surgeons performed the surgery using a standard surgical procedure. A muco-periosteal envelope or triangular flap was raised according to the surgeon's preference, bone removal and tooth sectioning was performed using a surgical hand-piece and burs as required, the respective tooth was elevated and interrupted sutures were placed to achieve wound closure (Vicryl Rapide®, Ethicon, Johnson & Johnson Medical Ltd., Norderstedt, Germany).

Following surgery patients received standard postoperative instructions and stayed at the investigational site for 6 hours for the assessment of pain (using a 0-100mm Visual Analogue Scale (VAS)), the amount of rescue medication consumed (i.e. 500mg paracetamol tablets) and the appearance of the surgical site regarding bleeding and assessment of the local irritancy and tolerability. After the observational period participants were discharged with a box of paracetamol and a postoperative diary to record their pain levels, analgesic and other concomitant medication consumption and adverse events (AEs) on a daily basis for one week.

Patients were asked to return for two follow-up visits on day 2 and 7 after surgery (=visits 3 and 4) during which post-surgical extra-oral swelling and trismus, as well as wound healing were assessed and rescue medication consumption was verified.

Baseline/Surgical Data

Demographic and lifestyle data were collected at the screening visit, including age, gender, ethnicity, weight, height and Body Mass Index (BMI). On the day of surgery some surgical measurements were collected, i.e. which LM3 was removed (left/right), whether the tooth was removed completely (yes/no), preoperative LA dose (in mL), supplemental LA dose (in mL), amount of bone removal (minor/moderate/severe), tooth sectioning (yes/no), raising of lingual flap (yes/no) and duration of surgery (in min).

Prespecified analysis plan

- Intention-To-Treat (ITT)= all randomised patients receiving ≥one study medication dose and with ≥one post-baseline efficacy evaluation;
- Per-Protocol (PP)= all ITT population patients without major protocol violation;
- Safety Population= all randomised patients receiving the study intervention.

Outcome measures and statistical analyses

The following secondary endpoints were evaluated:

- AUC of pain scores over the 12-hour-observation period post-surgery (assessed at the end of surgery, at 15mins intervals for the 6-hour-observation period on clinic and hourly for 6 hours after discharge), using an ANOVA model;

- Time to onset of pain (=pain ≥30mm on VAS) and time to RM, using survival analysis;
- Extra-oral swelling (=distance between lower border of tragus and a point in the midline, 3cm below vermilion border of lower lip, marked in removable ink on patient's chin) and trismus (=distance between left upper and lower incisor at maximal opening, assessed using a ruler) 6 hours post-surgery, on day 2 and day 7, using an ANOVA model;
- Peak-Pain-Intensity (=highest pain intensity during the 12-hour-observation period post-surgery) and RM consumption, using an ANOVA model;
- Cumulative proportions of patients using RM over the 6-hour-in-clinic-observation period, using chi-square test;
- AE comparisons (reported as description of event, intensity (mild/moderate/severe), seriousness (serious/non-serious), date of onset/end, expectation (expected/unexpected) and correlation with study treatment (certain/probable/possible/unlikely/not related/not assessable)), using Fisher's exact test.

Appendix Table 1: AEs and ADRs occurring after injection of study medication (safety population)

Variable	5mg (n=15)	12.5mg (n=15)	25mg (n=15)	50mg (n=14)	Placebo (n=16)	Total (n=75)
Adverse Events (AEs[a])						
Total number of AEs	23	20	25	9	15	92
Patients with at least one AE (N, %)	8 (53.3%)	9 (60%)	8 (53.3%)	5 (35.7%)	6 (37.5%)	36 (48%)
Adverse Drug reactions (ADRs[b])						
Total number of ADRs	2	3	9	2	0	16
Patients with ADRs (N, %)	2 (13.3%)	2 (13.3%)	5 (33.3%)	2 (14.3%)	0 (0%)	11 (14.6%)

a AEs = Adverse Event

b ADRs = Adverse Drug Reaction

Appendix Table 2: AEs classified by PT (=preferred patient term)

AE[a] description	5mg n=15	12.5mg n=15	25mg n=15	50mg n=14	Placebo n=16
Diarrhoea	1 (=7%)	0	0	0	1 (=6%)
Nausea	1 (=7%)	0	0	1 (=7%)	2 (=13%)
Vomiting	2 (=13%)	1 (=7%)	2 (=13%)	0	1 (=6%)
Dizziness	0	1 (=7%)	1 (=7%)	0	0
Headache	4 (=27%)	1 (=7%)	2 (=13%)	1 (=7%)	2 (=13%)
Jaw pain	1 (=7%)	4 (=27%)	0	0	2 (=13%)
Injection site pain	2 (=13%)	2 (=13%)	5 (=33%)	1 (=7%)	0
(Injection site) swelling	2 (=13%)	0	2 (=13%)	0	0
Flap necrosis	0	0	1 (=7%)	1 (=7%)	0
Wound infection	1 (=7%)	1 (=7%)	1 (=7%)	0	1 (=6%)
Gingival bleeding	1 (=7%)	0	1 (=7%)	0	0

[a] AE = Adverse Event

Appendix Table 3: ADRs classified by PT (=preferred patient term)

ADR[a] description	5mg n=15	12.5mg n=15	25mg n=15	50mg n=14	Placebo n=16
Flap necrosis	0	0	1 (=7%)	1 (=7%)	0
Injection site pain	2 (=13%)	2 (=13%)	5 (=33%)	1 (=7%)	0
Injection site swelling	0	0	2 (=13%)	0	0

[a] ADR = Adverse Drug Reaction