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ORIGINAL ARTICLE

Analgesic effectiveness of prophylactic therapy and continued therapy with naproxen sodium post simple extraction.

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Abstract: To compare the analgesic effectiveness of the prophylactic therapy and continued therapy with naproxen sodium after a simple dental extraction. Material and methods: This prospective randomized, parallel, single-blind clinical trial was developed in the Dental Clinic of the Universidad Alas Peruanas in Trujillo (Peru). The patients, who required simple extraction due to dental caries, were randomly distributed into three groups: 30 of them took 550mg naproxen sodium in the preoperative period and then every 12 hours, other 30 took 550mg naproxen sodium in the postoperative period and then every 12 hours, and 30(control group), received 400mg ibuprofen in the postoperative period and then every 8 hours, depending on the established criteria. The procedure was standardized, analgesic effectiveness was assessed by visual analog scale and the presence of adverse drug reactions was evaluated as well. Data were analyzed using ANOVA and Duncan's test using IBM SPSS 22 with a significance level of 5%. Results: Continued therapy with naproxen sodium showed greater analgesic effectiveness after a simple extraction at 1, 8 and 24 hours ($p<0.005$). Conclusion: Continued therapy with naproxen sodium presented greater effectiveness than prophylactic therapy with naproxen sodium after a simple extraction.

Keywords: *Analgesics; naproxen; tooth extraction.*
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INTRODUCTION.

The most accepted definition of pain is provided by the International Association for the Study of Pain (IASP). It is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1,2].

Managing postoperative pain is a critical component in daily dental practice and it is important for the effective use of healthcare resources[3,5]. When the pain is not adequately treated, it causes patients to worry and feel isolated, prevents sleep, leads to exhaustion and affects apetite[6]. The professional must be prepared to eliminate or minimize the pain with simple measures that are readily available, economical and have minimal or no adverse effect[4].

Due to the effectiveness of NSAIDs (nonsteroidal anti-inflammatory drugs) for reducing mild to moderate pain, they are frequently prescribed in dental practice[3]. Their mechanism of action involves the inhibition of cyclooxygenase activity (COX), thus eliminating the formation of inflammatory mediators. COX has two known isoenzymes, COX-1 and COX-2, and most of NSAIDs inhibit both in a non-selective way[7].

Among NSAIDs, ibuprofen has more than 45 years of clinical history and its safety profile has been widely studied. For this reason, it is used as control drug in oral surgery, became the first NSAID for sale without a pres-

cription and is associated with a lower risk of serious upper gastrointestinal complications[8].

Naproxen, like ibuprofen, is a propionic acid derivative NSAID that inhibits COX1 and COX2. It is completely absorbed when given by mouth and its plasma half-life is 14 hours[9]. It is effective in the treatment of pain resulting from dental and surgical procedures and its effect has greater duration than most of NSAIDs[10]. Thus, the need to make naproxen a painkiller of more rapid onset, has allowed the development of the sodium salt of naproxen[10,11].

On the other hand, extractions generate trauma in the periodontium, which leads to the perception of pain, but such effect can be counteracted by administrating NSAIDs before surgery[12], under the concept that alleviating pain is more difficult and slow than preventing its emergence[10,13]. This scheme, called analgesic prophylaxis, allows reducing the duration and severity of postoperative pain[10,12].

The prophylactic schema for pain management is based on pathophysiological and biochemical arguments, propionic being the most appropriate for this. For this reason, it is suggested that administrating substances that limit prostaglandin synthesis and release in the damaged tissues minimizes hyperalgesia and edema[14].

Laboratory experiments have shown that it is possible to manage postoperative pain with preemptive analgesia; however, clinical trials have not shown conclusive evidence in relation to this. Therefore, these studies are required to evaluate the effectiveness of preventive analgesic interventions[15] because clinical results are not conclusive yet. For this reason, it was decided to compare the analgesic effectiveness of prophylactic therapy and continued therapy with naproxen sodium after a simple extraction.

MATERIAL AND METHODS.

This was a randomized parallel single-blind study design phase IV clinical trial conducted in the Dental Clinic of the Universidad Alas Peruanas in Trujillo, from November 2013 until July 2014. The sample population consisted of 30 patients per group. For calculating sample size, the formula for comparing means was used under the following parameters: $Z\alpha$=1.645 (value for Z at 5% type I error), $Z\beta$=1.28 (value for Z at 10% type II error) $\mu 1$ =50.05 (effectiveness of continued therapy with naproxen sodium during one hour following the extraction[1]) $\mu 2$ =54.05 (effectiveness of continued therapy with ibuprofen one hour after extraction[1]), σ=6.15 (standard deviation of the effectiveness of continued therapy with naproxen sodium one hour following the extraction 1).

The study included ASA I patients between 18 and 45 years old, who had complete their primary education and had a prior tooth extraction history. They had indication of simple extraction due to dental caries in a multirooted tooth (except third molars) or two adjacent eutopic, asymptomatic with null or mild bone resorption single-rooted teeth. Patients who refused to participate, those with contraindications for tooth extraction and the use of local anesthetic (lidocaine) with epinephrine and/or the administration of the drugs under study, those with intellectual disability and pregnant or lactating women, and those who did not use an appropriate form of contraception were excluded from the study. Also, patients who had received anesthesia, sedatives, pain relievers, tricyclic antidepressants, corticosteroids, anticonvulsants, phenothiazines, alcohol, or caffeine 48 hours before the surgery were excluded.

Once the study started, sampling unit were eliminated if it had not been possible to work with the standardized procedure, if the patient registered a score higher than 70 mm for pain on VAS for the anaesthetic injection before the extraction, if more than two cartridges of anesthesia were used for the procedure, if the intervention (from syndesmotomy until compression) exceeded 20 minutes, if the patient failed to comply with the indications, if the instrument was not correctly filled in, if the patient did not show up for the follow-up appointment or if there was any postoperative complication.

For the execution, we counted with the approval of the Graduate School from the Universidad Nacional de Trujillo and the Management of the School of Dentistry

of the Universidad Alas Peruanas in Trujillo (Letter No. 022-2014-EAPE-UAP-TRUJILLO). The ethical principles of the Declaration of Helsinki and the General Law of Health of Peru (Law No. 26842) were considered.

Prior to the procedure, the patient was explained about the importance of the study and, if they agreed to participate, they were asked to read and sign the informed consent.

The standardized procedure was executed by dental students undertaking the Stomatological Surgery I subject under the supervision of the principal investigator. For analgesic treatment, an external contributor randomly distributed patients in the following manner:

• Prophylactic therapy group: 550mg naproxen sodium (Farmindustria S.A. Batch 10233533) was administered by mouth 30 minutes before the procedure, then, every 12 hours for 4 doses.

• Continued therapy group: 550mg naproxen sodium (Farmindustria S.A. Batch 10233533) was administered by mouth 20 minutes after the procedure, then, every 12 hours for 4 doses.

• Control group: 400mg ibuprofen (Farmindustria S.A. Batch 10940154) was administered by mouth 20 minutes after the procedure, then, every 8 hours for 6 doses.

Patients received the measuring instrument and were trained to fill it correctly with the given instructions. They were also instructed to comply with the requirements of the study, and asked to return for the follow-up appointment (third day) with the blister of the prescribed drug and the measuring instrument. During the days of the study, they were forbidden to use antacids containing magnesium oxide or aluminum dioxide, steroid medications (except oral contraceptives), and in general any medication that could alter the evaluations. On the recommendation of Joshi *et al.*[16], telephone contact with the patient was kept at all times to monitor compliance of the indications and possible complications. If any patient had considered pain relief was insufficient, a rescue analgesic would have been indicated, and the case would have been analyzed according to the intention-to-treat principle.

The measurement instrument was a self-administered structured questionnaire. It recorded the intensity of pain on VAS 1, 8 and 24 hours after starting the medication. Additionally, patients were asked to report the presence of adverse drug reactions (ADR). Data were analyzed using ANOVA and Duncan's test with IBM SPSS statistics[22]. The transformation, ln(y+1), was used to achieve homogeneity of variances, which was found with Levene's test. The effectiveness of the therapies was considered different if $p<0.05$.

RESULTS.

In the present study, a total of 93 patients were evaluated, 58 were female and 35 male, whose ages ranged between 21 and 44 (mean=35.70). Three patients with alveolitis were excluded.

As it can be seen in Table 1, one hour post simple extraction, the level of pain of continued therapy with naproxen sodium was 1.83±1.70 and the one of the prophylactic therapy was 5.20±3.99, compared with the one of ibuprofen which was 6.60±4.47. ANOVA indicated that there was a difference between the three therapies ($p=0.002$) and Duncan's test showed that there was a difference between continued therapy with naproxen sodium, prophylactic therapy with the same drug and with ibuprofen.

As it can be seen in Table 2, 8 hours post simple extraction, the level of pain of continued therapy with naproxen sodium was 1.77±2.03 and for the prophylactic therapy was 7.57±4.37, compared with ibuprofen was 7.87 ±9.00. ANOVA indicated that there was a difference between the three therapies ($p=0.000$), and Duncan's test showed that there was a difference between continued therapy with naproxen sodium, prophylactic therapy with the same drug and with ibuprofen.

As it can be seen in Table 3, 24 hours post simple extraction, the level of pain of continued therapy with naproxen sodium was 4.00±3.71 and for the prophylactic therapy was 7.80±4.86, compared with ibuprofen which was 6.90±5.01. ANOVA indicated that there was no

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Table 1. Analgesic effectiveness of therapy with naproxen sodium 1 hour post simple extraction.

		Continued therapy with naproxen sodium	Prophylactic therapy with naproxen sodium	Ibuprofen
Original	Media	1.83	5.20	6.60
	Standard D.	1.70	3.99	4.47
Transformed	Media	0.898	1.429	1.730
	Standard D.	0.714	0.974	0.936
ANOVA: F		6.852		
P		0,002<0.05		
Duncan's Test *		a	b	b

* There is no difference between therapies with the same letter (p>0.05). Levene's test (p=0.183 >0.05).

Table 2. Analgesic effectiveness of therapy with naproxen sodium at 8 hours post simple extraction.

		Continued therapy with naproxen sodium	Prophylactic therapy with naproxen sodium	Ibuprofen
Original	Media	1.77	7.57	7.87
	Standard D.	2.03	4.37	9.00
Transformed	Media	0.813	1.788	1.775
	Standard D.	0.797	1.025	1.007
ANOVA: F		10.433		
P		0,000<0.05		
Duncan's Test *		a	b	b

* There is no difference between therapies with the same letter (p>0.05). Levene's test (p=0.691 >0.05).

Table 3. Analgesic effectiveness of therapy with naproxen sodium at 24 hours post simple extraction.

		Continued therapy with naproxen sodium	Prophylactic therapy with naproxen sodium	Ibuprofen
Original	Media	4.00	7.80	7.87
	Standard D.	3.71	4.86	9.00
Transformed	Media	1.292	1.867	1.640
	Standard D.	0.946	1.001	1.006
ANOVA: F		2.492		
P		0,089<0.05		
Duncan's Test *		a	b	b

* There is no difference between therapies with the same letter (p>0.05). Levene's test (p=0.691 >0.05).

difference between the three therapies (p=0.089), and Duncan's test showed that there was a difference between therapies with naproxen but not with the control. None of the patients reported ADR during the evaluation.

DISCUSSION.

Pain is a complex subjective experience, and there is no tool to measure it objectively. In general, dimensional scales are used in pain research and they only measure the sensory component. The visual analogue scale (VAS), verbal rating scale (VRS), and numerical scale of pain (NRS) are the most known and commonly preferred. VAS allows the use of parametric tests and therefore is widely used in scientific research[17].

The dental pain model is widely used to evaluate the effectiveness of analgesic agents. This model is characterized by localized pain that is predictable in its nature, duration (3-5 days) and intensity (moderate to severe)[18]. However, studies on prophylactic analgesia in oral surgery mainly relate to extraction of third molars. This pain is different from simple extraction, because it produces greater trauma, moderate to severe pain intensity, edema and generally lockjaw. In these studies, the results are conflicting, so Savage *et al.*[19] argued that, even though preemptive analgesia has been demonstrated repeatedly in animal models of pain, clinical evidence supporting its use in humans has been more variable. Since they consider different models of pain, as well as other NSAIDS, it is not considered relevant to discuss these studies.

The present study was done considering what was found in the study by Asmat *et al.*[1]. It compares paracetamol and naproxen sodium, the latter presented greater effectiveness for controlling pain after a simple extraction, even in the control group (ibuprofen).

The only study on simple extractions was done by Aravena *et al.*[12], who reported similar results to those found in this study. These researchers conducted a randomized double blind placebo-controlled clinical trial in 54 patients. These were randomly assigned into two groups: one received lysine clonixinate (LC) as prophylactic therapy and the other was given placebo. It was concluded that, prophylaxis with LC analgesic did not prove to be more effective in reducing pain after dental extractions in comparison to the use of placebo and postoperative doses.

No patient reported ADR in the present study, likely due to using doses over a short period of time.

Variability of the results of clinical studies on preemptive analgesia in humans has been disappointing because the proposed concept is logical and there is a need to improve management of pain associated with surgical procedures[19].

Taking into consideration what Dias says[20], that postoperative pain resulting from elective surgical procedures remains during a 24-hour period and the duration of treatment with COX inhibitors must be established for a maximum period of 48 hours, it was proceed to evaluate patients in the first 24 hours after the extraction.

It is considered a limiting factor of this study that the extractions were performed by students of stomatology who exhibit different motor skills. However, this error was controlled by the random assignment in groups and the strict supervision of the standardized procedure by the researchers, thus, this factor is considered as part of the random error that is present in all the investigations using sampling.

Further studies are required in this regard, mainly at the molecular level, to determine in which cases and with what type of pain medication prophylactic therapy recommendation is feasible, thus provide evidence-based pharmacotherapy guidelines for dentistry.

CONCLUSIONS.

It can be concluded that:

1. The analgesic effectiveness of continued therapy with naproxen sodium 1 and 8 hours post simple extraction was higher than prophylactic therapy with naproxen sodium and ibuprofen (control).
2. The analgesic effectiveness of continued therapy with naproxen sodium 24 hours post simple extraction

was higher than prophylactic therapy with naproxen sodium, but not with ibuprofen (control).

3. There were no adverse reactions reported for the use of naproxen sodium and ibuprofen during the study.

Efectividad analgésica post exodoncia simple de la terapia profiláctica y la terapia continuada con naproxeno sódico.

Resumen: Objetivo: Comparar la efectividad analgésica post exodoncia simple entre la terapia profiláctica y la terapia continuada con naproxeno sódico. Material y métodos: Ensayo clínico, prospectivo aleatorizado, paralelo y simple ciego, se desarrolló en la Clínica Estomatológica de la Universidad Alas Peruanas Filial Trujillo (Perú). Los pacientes, quienes requerían exodoncia simple por caries dental, fueron distribuidos aleatoriamente en tres grupos: 30 recibieron naproxeno sódico 550 mg en el preoperatorio y luego cada 12 horas, 30 recibieron naproxeno sódico de 550 mg en el postoperatorio y luego cada 12 horas y, 30, ibuprofeno (grupo testigo) de 400 mg en el posoperatorio y luego cada 8 horas, según los criterios establecidos. El procedimiento fue estandarizado, evaluándose la eficacia analgésica, mediante la escala visual analógica, y la presencia de reacciones adversas medicamentosas. Los datos fueron analizados mediante el ANOVA y el test de Duncan empleando IBM SPSS Statistics 22. Resultado: La terapia continuada con naproxeno sódico presentó mayor efectividad analgésica post exodoncia simple a las 1, 8 y 24 horas (p<0,005). Conclusión: la terapia continuada con naproxeno sódico presentó mayor efectividad que la terapia profiláctica con naproxeno sódico post exodoncia simple.

Palabras clave: *Analgésicos; naproxeno; extracción dental.*

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