Journal of Oral Rehabilitation

Journal of Oral Rehabilitation 2015 **42**; 209–219

Chlorhexidine gel and less difficult surgeries might reduce post-operative pain, controlling for dry socket, infection and analgesic consumption: a split-mouth controlled randomised clinical trial

A. HARAJI* & V. RAKHSHAN†‡ *Department of Oral and Maxillofacial Surgery, Dental Branch, Islamic Azad University, Tehran, †Iranian Tissue Bank and Research Center, Tehran University of Medical Sciences, Tehran and ‡Department of Dental Anatomy and Morphology, Dental Branch, Islamic Azad University, Tehran, Iran

SUMMARY **Reports on post-surgical pain are a few, controversial and flawed (by statistics and analgesic consumption). Besides, it is not known if chlorhexidine can reduce post-extraction pain adjusting for its effect on prevention of infection and dry socket (DS). We assessed these. A total of 90 impacted mandibular third molars of 45 patients were extracted. Intra-alveolar 0·2% chlorhexidine gel was applied in a split-mouth randomised design to one-half of the sockets. None of the included patients took antibiotics or analgesics afterwards. In the first and third post-operative days, DS formation and pain levels were recorded. Predictive roles of the risk factors were analysed using fixed-effects (classic) and multilevel (mixed-model) multiple linear regressions ($\alpha = 0{\cdot}05$, $\beta \leq 0{\cdot}1$). In the first day, pain levels were $5{\cdot}56 \pm 1{\cdot}53$ and $4{\cdot}78 \pm 1{\cdot}43$ (out of 10), respectively. These reduced to $3{\cdot}22 \pm 1{\cdot}41$ and $2{\cdot}16 \pm 1{\cdot}40$. Pain was more intense on the control sides [both *P* values = 0·000 (paired *t*-test)]. Chlorhexidine had a significant pain-alleviating effect ($P = 0{\cdot}0001$), excluding its effect on DS and infection. More difficult surgeries ($P = 0{\cdot}0201$) and dry sockets were more painful ($P = 0{\cdot}0000$). Age had a marginally significant negative role ($P = 0{\cdot}0994$). Gender and smoking had no significant impact [$P \geq 0{\cdot}7$ (regression)]. The pattern of pain reduction differed between dry sockets and healthy sockets [$P = 0{\cdot}0102$ (ANOVA)]. Chlorhexidine can reduce pain, regardless of its infection-/DS-preventive effects. Simpler surgeries and sockets not affected by alveolar osteitis are less painful. Smoking and gender less likely affect pain. The role of age was not conclusive and needs future studies.**

KEYWORDS: **tooth extraction, impacted teeth, post-operative pain, risk factors, chlorhexidine gel**

Accepted for publication 16 August 2014

Introduction

Surgical removal of impacted mandibular third molars often accompanies post-operative complications such as pain, trismus, infection or dry socket (DS) (1, 2). Pain is one of the most common and important post-operative complications (2–4), and can cause many patients to avoid seeking treatment (5). It is also the most important symptom of dry socket (6, 7). If dry socket and/or infection do not occur, a moderate pain peaks within the first 24 post-operative hours and then reduces quickly (4, 5, 7–9). If dry socket happens, the post-surgical pain will differ in pattern; it will intensify between the second and fourth post-surgical days (6, 7, 10–14).

Control of post-operative pain is a crucial part of practice (3). Different measures have been proposed for this purpose, including systemic analgesic con-

doi: 10.1111/joor.12230

sumption, irrigation with different agents and using analgesic/tranquiliser dressings (6–8, 10–12, 14). Also the application of chlorhexidine (CHX) gel might reduce post-extraction pain (7).

Additionally, knowing the risk factors of pain can aid the clinician in identifying high-risk patients (1), individualising the treatment plan (4), exercising more conservative protocols for high-risk patients (6, 10) and informing the patient (15). However, the risk indicators of post-operative pain are quite debated (14, 16).

There are only a few controversial studies focused on the risk factors of pain (1, 3, 4, 17). Most of these researches lack prospective, split-mouth, multivariable designs (in which other factors can be adjusted for) (1, 15). Further, while assessing the risk factors, no study has distinguished the pain of dry socket or infection from the routine habitual post-surgical pain. Moreover, the interactions of risk factors with each other and with potential pain-alleviating interventions have never been estimated except in a study concerning the risk factors but not treatments (1). Finally, all previous studies have assessed the pain while the included patients ingested painkillers (1, 16, 18), a factor known as an inherent confounder to the perceived pain (7, 13, 16).

In view of the mentioned debates and shortcomings, as well as the lack of any multivariable studies on the pain-reducing effect of CHX, or the lack of any split-mouth (highly matched) studies on risk factors of pain, and the absence of any assessments of the interactions of pain risk factors and treatments, this analysis was conducted. Its purpose was to assess within a multivariable context, the role of potential predictors of post-operative pain (and their interactions), controlling for confounders such as dry socket, infection and analgesic consumption.

The null hypotheses were as follows: (1) none of the predictors (age, gender, smoking, difficulty of surgery, dry socket and CHX treatment) influences the pain levels. (2) The prognostic factors do not alter the effects of each other (i.e. there are no interactions). (3) Dry socket pain does not differ in severity from the routine post-surgical pain. (4) The pain perceived 1 day after the surgery does not differ from the pain sensed 3 days after the surgery. (5) The pattern of pain alterations over time (if any) does not differ between dry sockets and intact sockets.

Subjects and methods

This double-blind split-mouth randomised controlled clinical trial was performed on 90 extraction sockets of bilateral impacted mandibular third molars in 45 patients attending a private clinic (2011–2012) (7, 19). The sample size (two sets of 45 highly matched sockets) sufficed to obtain test powers >0·9 for the comparison of matched placebo and experimental groups.

Inclusion and exclusion criteria

To be included in the study, patients had to be preferably 18–45 years old, needing bilateral extraction of impacted mandibular third molars with a difficulty index preferably above 7 according to the Pederson scale (equal on both the treatment/control sides in each patient) (7, 19, 20). Patients were excluded if they were unwilling to participate or attend the follow-up sessions, if they had any systemic or mental diseases, had any symptoms during the 10 days prior to the surgery, had any condition contraindicative of surgery, had ingested any medications as of 4 days before the operation, needed antibiotic prophylaxis, were pregnant, had pain-inducing conditions or had any allergies (7). The internal review board of the university approved the protocol ethics, according to the Helsinki Declaration. Written consents were taken from the participants (7, 19). During the explanation of the study to the patients, they were briefed that the investigators needed patients that could tolerate pain without taking analgesics. They were asked if they could do it. However, they were assured that their refusal would not affect by any means the treatments provided to them. All patients would be provided proper routine post-surgical care, including analgesic prescription (upon their request or need) or antibiotic treatment (in the case of clinical need determined by the surgeon). However, the patients taking such medications until the third day would be excluded from the study. This was because antibiotic consumption (indicating a post-operative infection which might alter the pain) and analgesic ingestion (which might affect the pain as well) (7, 13, 16) were strong confounders. Only the information regarding patients who did not need or ask for analgesics or did not clinically need antibiotics until the third day would be included. If any infections happened after the study period (after the third day) and the patient had not consumed any analgesics or antibiotics over

the study period, they would be given proper antibiotic medication while being still included in the study. As stated above, proper care would be provided to the excluded patients as well (7).

More than 200 subjects were evaluated. Most of the patients meeting the other inclusion criteria disagreed to participate because of their intention to taking analgesics post-operatively. Of the patients who met the inclusion criteria and volunteered to participate, none was dropped out post-surgically due to any infection or analgesic/antibiotic consumption. However, four were dropped out after the surgery because of failure to attend the follow-up.

The experiments and clinical assessments

Surgery. Before the experiments, a general practitioner randomised the chlorhexidine treatment. A blinded maxillofacial surgeon (practicing for about 15 years) surgically removed both the mandibular third molars of each patient in a single session. The order of the extraction sites (left or right) was selected randomly unless patients asked for or needed clinically the removal of one side first. The patients underwent the procedure under local anaesthesia (articaine 4% epinephrine) administered to the inferior alveolar, long buccal and lingual nerves. Each patient received one carpule of anaesthesia on each side, first. The patient would receive additional dose(s) upon their need or request, until the surgery was totally painless. A mucoperiosteal pocket was cut and everted to gain access to the third molar, carrying out osteotomy and dental sectioning (using rotary instruments) when necessary. Once the tooth had been extracted, the alveolus was cleaned and the bone edges were smoothed. After the operation, the surgeon left the room. As the randomised treatment, the general dentist applied the 0·2% CHX gel* to one of the two same-sized ($14 \times 7 \times 7$ mm^3) dressings of gelatin sponge containing colloidal silver† for each patient. The placebo specimen would be a same-sized dry gelatin dressing. Then, the same operator placed the CHX/placebo gelatin sponges in the bilateral extraction sockets. The dentist gently pushed the dressings into the sockets and ensured the sponge reached the socket floor and that no excess gel was visible around the experimental socket. The dressing would be resorbed within four post-operative weeks. Both the surgeon and the patients were blinded of the random CHX allocations. The surgeon returned and sutured the wound (7, 19).

Assessment of pain and other variables. The pain was evaluated using a visual analogous scale (VAS). It was assessed on each side of each patient. The evaluations were performed at the office, on both the first and the third post-operative days (about 24 and 72 h after the surgery, respectively) (7, 8, 17). The VAS was converted to 10 distances of equal length, each starting from the ranks 0 to 9 (score 0: no pain, score 10: intolerable pain).

The blinded maxillofacial surgeon diagnosed the dry socket occurrence in the third post-operative day, according to the Blum's standardised criteria (7, 10, 19). Demographic data (age and gender) as well as patients' smoking habit (yes/no) were recorded. The variable 'smoking habit' was regarded as 'yes' if the patients reported that they were smokers. This included patients who were smokers but had not smoked before the surgery.

Statistical analyses and the reliability of the pain reports

There were excellent intra-rater agreements between the reports of the patients at the first and second sessions, regarding the pain they sensed on their placebo side (Cronbach $\alpha = 0{\cdot}927$, $P = 0{\cdot}0000$) and on their CHX side ($\alpha = 0{\cdot}944$, $P = 0{\cdot}0000$).

Descriptive statistics were calculated. All the independent variables except for dry socket were equal on both the placebo/CHX sides (because of the split-mouth design of the study). The control and treatment groups were compared in terms of dry socket formation, using a McNemar matched pairs test (Table 1) (19). The data were analysed using a paired *t*-test, repeated-measures two-way analysis of variance (ANOVA), Spearman correlation coefficient, fixed-effects (classic) multiple linear regression and hierarchical multilevel (mixed-model) multiple linear regression analyses (random intercept and slopes included). The level of significance was set at 0·05.

Results

The sample consisted of 90 bilateral extraction sockets in 45 patients. The subjects were 24 men and 21

*Kimia, Tehran, Iran.

†Gelatamp, Roeko, Germany.

Table 1. Net and frequency (%) distributions of 45 matched pairs of bilateral extraction sockets (in 45 patients) according to the dry socket (DS) occurrence in patients' experimental and control sides

DS in the Placebo side	DS in the CHX side			
	Negative	Positive	Total	*P*
Negative	29 (64·4)	0	29 (64·4)	
Positive	10 (22·2)	6 (13·3)	16 (35·6)	0·002
Total	39 (86·7)	6 (13·3)	45 (100)	

The *P*-value is calculated using the McNemar test, by comparing the frequency of the independent variable 'dry socket' in the control versus experimental matched sides.
All other independent variables are equal and matched between the placebo and treatment groups.

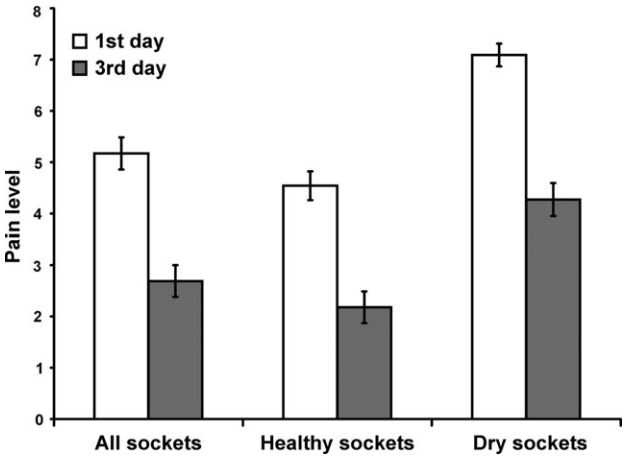

Fig. 1. Mean (and 95% CI) of pain intensities in dry sockets (n = 22), healthy sockets (n = 68) and the sample (n = 90 alveoli).

women. Patients' mean ages were 22·6 ± 2·9 (Range: 18–31) in men and 21·5 ± 2·6 (Range: 17–26) in women. Of the participants, 16 men and 5 women smoked cigarettes. The difficulty indices were 7·0 ± 0·8 (Range: 6–8) in men and 7·3 ± 0·7 (Range: 6–8) in women.

There were moderate to strong positive correlations between the pain levels perceived on both sides in the first day (ρ = 0·658, P = 0·000) and in the third day (ρ = 0·464, P = 0·001).

The difference between the pain perceived on the matched experimental and placebo sides on each post-operative day (determined in a bivariable framework)

According to the paired t-test (n = 90 matched sockets), on each of the post-surgical days, there was a significant difference between the pain perceived on the placebo and CHX sides (Fig. 1, Table 2). The application of chlorhexidine gel could significantly reduce pain intensities either on the first post-operative day or on the third day (Fig. 1, Table 2).

Differences in the pain of dry sockets versus healthy sockets as well as the pattern of pain reduction over time with and without dry socket occurrence

The repeated-measures two-way ANOVA (n = 180 observation: 90 sockets at two time points) showed that the pain was greater in dry sockets compared to intact sockets (P = 0·0000). It was more severe on the first day compared to the third day (P = 0·0000, Fig. 1). The interaction of 'dry socket' and 'time' variables was significant as well (P = 0·0102). This meant that the pattern of pain reduction over time differed between healthy and dry sockets.

Table 2. Pain intensities in the first and third post-surgical days, on the matched control and treatment sides

Day	Group	Mean pain	SD	Interquartile range					95% CI		*P*
				Min	Q1	Med	Q3	Max	Low	Up	
1st day	Placebo	5·56	1·53	3	4	6	7	8	5·096	6·015	0·000
	CHX	4·78	1·43	2	4	5	5·5	8	4·349	5·207	
3rd day	Placebo	3·22	1·41	0	2	3	4	6	2·888	3·703	0·000
	CHX	2·16	1·40	0	1	2	3	5	2·102	2·873	

SD standard deviation of pain levels; Min, minimum pain level; Q1, 25th percentile; Med, median; Q3, 75th percentile; Max, maximum pain level; CI, confidence interval for the mean pain level; Up, upper CI bound; Low, lower CI bound.
The *P*-values are calculated using the paired *t*-test, comparing the pain levels on the treatment side (CHX) versus the control side (Placebo). The comparisons are performed for both post-operative days.
Pain levels are unitless, recorded on a 0–10 scale. Zero means no pain; ten means intolerable pain.

The bivariate correlations between pain and the independent variables

The significant correlation coefficients between the independent variables and pain are presented in Table 3.

Prognostic factors of pain, determined in a multivariable framework

On each side and each session separately (excluding the variable CHX). To eliminate multicollinearity between the main variables and their interactions – which could disrupt the results – each variable was mean-centred before its inclusion in the model. Still, some interaction terms led to rather high variance inflation factors. They were excluded. The significant predictors determined by fixed-effects (classic) regression models are exhibited in Table 4.

On both sides combined (accounting for the variable CHX and the random effects). The significant variables (determined by mixed-model regressions) in the 1st and 3rd day (accounting for the matching), as well as those in both days combined (accounting for the matching and repeated measures) are presented in Table 5.

Discussion

The findings of this study indicated that post-operative pain was more intense after difficult surgeries and in dry sockets. CHX application could reduce pain, adjusted for its preventive effect on dry socket and infection within the evaluated period (until the third day).

Each significant interaction indicated that two prognostic factors might alter the effects of each other. The coefficient signs of the interaction terms pointed to the direction of this modification. The positive interactions (i.e. male gender by CHX application, age by dry socket in the third day) denoted that the predictors might intensify each other's influence. Therefore, the pain-alleviating effect of chlorhexidine might be weaker in men. In addition, the pain caused by dry sockets in the third day might be more intense in older patients. The negative interactions (i.e. the operation difficulty by dry socket, age by CHX application in the third day) denoted that each factor tended to reduce the impact of the other one: The pain-alleviating effect of CHX in the third day was less visible in older people. As well, pain of dry socket tended to be more intense in less difficult surgeries. A better explanation for the same interaction is that the non-DS pain was greater in surgeries that were more difficult.

Chlorhexidine, available as mouth rinse and topical gel, is a biguanide antiseptic shown effective in the prevention of dry socket (7, 10, 11, 13, 19). Our multivariable analyses confirmed that chlorhexidine gel might have therapeutic effects on reduction of post-surgical pain, even in the absence of any clinical

Table 3. Spearman coefficients between pain intensities and the independent variables

		Control (n = 45)		Treatment (n = 45)		Both sides (n = 90)	
Day	Independent variable	ρ	P	ρ	P	ρ	P
1st day	Sex: male	−0·098	0·522	0·042	0·784	−0·029	0·783
	Age	−0·115	0·453	−0·180	0·236	−0·141	0·184
	Difficulty	0·273	0·070	**0·447**	**0·002**	**0·323**	**0·002**
	Smoking: positive	−0·108	0·481	−0·137	0·371	−0·118	0·270
	Dry socket: positive	**0·739**	**0·000**	**0·663**	**0·000**	**0·723**	**0·000**
	CHX gel: positive	–	–	–	–	**−0·257**	**0·015**
3rd day	Sex: male	−0·138	0·365	−0·024	0·877	−0·076	0·477
	Age	0·053	0·728	**−0·294**	**0·050**	−0·111	0·296
	Difficulty	0·240	0·112	**0·422**	**0·004**	**0·282**	**0·007**
	Smoking: positive	−0·085	0·579	−0·138	0·368	−0·104	0·330
	Dry socket: positive	**0·646**	**0·000**	**0·476**	**0·001**	**0·605**	**0·000**
	CHX gel: positive	–	–	–	–	**−0·358**	**0·001**

ρ, Spearman correlation coefficient.
Significant results in bold.

Table 4. The role of the pain predictors (excluding CHX) and their interactions on the pain levels on each side at each session computed within fixed-effects (classic) multiple linear regression frameworks

Side	Day	Predictor	B	SE	Beta	*P*
Placebo	1st day	Male sex	−0·550	0·323	−0·181	0·097
	AR = 0·657	Age	−0·084	0·055	−0·151	0·135
	(*n* = 45 sockets)	Difficulty	0·651	0·200	**0·334**	**0·002**
		Smoking: yes	0·363	0·354	0·120	0·311
		Dry socket: yes	2·544	0·306	**0·804**	**0·000**
		Difficulty × DS	−1·011	0·381	**−0·275**	**0·012**
		Smoking × DS	−0·881	0·632	−0·143	0·172
		Male sex × smoking	0·510	0·672	0·075	0·453
	3rd day	Male Sex	−0·681	0·377	−0·243	0·079
	AR = 0·452	Age	0·024	0·063	0·047	0·705
	(*n* = 45 sockets)	Difficulty	0·477	0·231	**0·266**	**0·046**
		Smoking: yes	0·219	0·412	0·078	0·598
		Dry socket: yes	1·968	0·332	**0·675**	**0·000**
		Difficulty × DS	−0·636	0·431	−0·188	0·149
		Smoking × DS	−0·808	0·732	−0·142	0·277
CHX	1st day	Male sex	0·328	0·352	0·116	0·357
	AR = 0·517	Age	−0·113	0·061	−0·216	0·073
	(*n* = 45 sockets)	Difficulty	0·568	0·215	**0·305**	**0·012**
		Smoking: yes	−0·307	0·349	−0·108	0·384
		Dry socket: yes	2·633	0·477	**0·634**	**0·000**
		Male Sex × difficulty	−0·438	0·435	−0·113	0·321
		Male sex × DS	−0·502	0·993	−0·062	0·616
	3rd day	Male sex	0·179	0·387	0·064	0·647
	AR = 0·341	Age	−0·157	0·068	**−0·308**	**0·026**
	(*n* = 45 sockets)	Difficulty	0·511	0·241	**0·281**	**0·040**
		Smoking: yes	−0·076	0·396	−0·027	0·849
		Dry socket: yes	1·745	0·528	**0·429**	**0·002**

B, regression coefficient; SE standard error; Beta, standardised regression coefficient; DS, dry socket; CHX, chlorhexidine; AR, adjusted R-squared for the model.

Variable references: Positive coefficient signs of gender, smoking and dry socket indicate a greater pain in 'males', 'smokers' and 'dry sockets', respectively. The negative coefficient of CHX indicates a lower pain after CHX application. The positive correlations with difficulty index and age indicate more intense pain in surgeries that were more difficult and in older people. Significant results in bold.

infection or dry socket. This is not assessed before and is worth further investigations. Some research had confirmed the role of hygiene (8, 21) and antibiotic prophylaxis in pain reduction (16). Perhaps, the antiseptic quality of CHX might reduce painful inflammatory mediators that would be produced in response to bacterial activity. Further investigations are needed for confirming this.

There might be a relationship between the magnitude of post-operative pain with surgical trauma and bone removal, which release inflammatory activators (2, 9, 16). Such an influence was visible in this study and some other ones (4, 9, 22). Some investigators found significant links between the pain and the duration of operation (3), which could also postpone the recovery (4). However, some researchers did not find a significant influence of trauma on pain (2, 16). This might be due to usage of painkillers in their set-ups (as confounders) (16). The surgical difficulty can also increase the risk of dry socket (18, 19), which accompanies greater pain. However, the effect of dry socket was already adjusted for, in this analysis.

Nicotine might have both negative and positive effects on pain. It might reduce blood supply and thus increase pain (8). On the other hand, it might improve the pain threshold and tolerance (16). After several analyses, we did not find any significant effect of smoking on the pain. Many other studies as well did not find such an influence (2, 8, 16, 18). A study linked more severe pains to post-operative smoking but not to pre-operative smoking (8). Grossi

Table 5. Three hierarchical multilevel (mixed-model) multiple linear regression analyses of pain predictors (and their interactions) in the first and third post-operative days (n = 90 each) and in both sessions combined (n = 180). The dependent variables are the pain levels in the first and third days, as well as the pain intensity in both days together

Session	Predictor: Reference	B	SE	*P*	95% CI	
First day (n = 90 matched sockets)	Male sex	0·016	0·281	0·9558	−0·553	0·584
	Age	−0·083	0·049	0·0999	−0·183	0·017
	Difficulty	0·468	0·165	**0·0072**	0·134	0·802
	Smoking: positive	−0·124	0·290	0·6721	−0·711	0·463
	Dry socket: positive	2·294	0·240	**0·0000**	1·817	2·771
	CHX: positive	−0·244	0·146	0·1017	−0·539	0·050
	Male sex × CHX	0·616	0·275	**0·0309**	0·060	1·171
	Difficulty × DS	−0·478	0·272	0·0823	−1·020	0·063
Third day (n = 90 matched sockets)	Male sex	0·254	0·367	0·4939	−0·490	0·997
	Age	−0·030	0·061	0·6215	−0·153	0·093
	Difficulty	0·494	0·208	**0·0235**	0·071	0·917
	Smoking: positive	−0·266	0·356	0·4597	−0·989	0·457
	Dry socket: positive	1·589	0·304	**0·0000**	0·984	2·194
	CHX: positive	−0·658	0·169	**0·0004**	−1·000	−0·316
	Male sex × age	−0·099	0·124	0·4318	−0·350	0·153
	Male sex × difficulty	−0·551	0·473	0·2516	−1·509	0·407
	Male sex × CHX	0·513	0·334	0·1325	−0·162	1·187
	Age × difficulty	−0·108	0·077	0·1669	−0·263	0·047
	Age × DS	0·329	0·147	**0·0279**	0·037	0·622
	Age × CHX	−0·158	0·060	**0·0120**	−0·280	−0·037
	Difficulty × smoking	0·544	0·466	0·2494	−0·397	1·486
	Difficulty × DS	−0·530	0·321	0·1037	−1·171	0·111
Both sessions [n = 180 (90 matched sockets in two repeated-measures observations)]	Male sex	−0·048	0·281	0·8654	−0·616	0·520
	Age	−0·085	0·050	0·0994	−0·187	0·017
	Difficulty	0·394	0·163	**0·0201**	0·065	0·723
	Smoking: positive	−0·116	0·290	0·6916	−0·703	0·471
	Dry socket: positive	2·012	0·206	**0·0000**	1·604	2·419
	CHX: positive	−0·450	0·113	**0·0001**	−0·674	−0·226
	Male sex × DS	−0·593	0·447	0·1865	−1·475	0·290
	Male sex × CHX	0·611	0·261	**0·0209**	0·094	1·127
	Difficulty × DS	−0·604	0·237	**0·0119**	−1·073	−0·135
	Smoking × CHX	−0·383	0·242	0·1153	−0·861	0·095

B, regression coefficient; SE standard error; CI, confidence interval; DS, dry socket; CHX, chlorhexidine.
Variable references: positive coefficient signs of sex, smoking and dry socket indicate a greater pain in 'males', 'smokers' and 'dry sockets', respectively. The negative coefficient of CHX indicates a lower pain after the CHX application. The positive correlations with difficulty index and age indicate greater pains in more difficult surgeries and in older people. Significant results in bold.

et al. (16). observed higher levels of pain in smoker females but not in the total sample. They suggested that probably the positive effects of smoking appear in men while its negative influence are more obvious in women (16). We accounted for the role of gender as well as its interaction with smoking, and again found no associations. It seems that smoking might have no or limited impact on post-operative pain. Few studies have been performed in this regard, and future researches taking into account the *dose* of smoking seem necessary.

Owing to biological and psychological differences, females and males might perceive and respond differently to sensory and pain stimuli as well as pain medication (16, 23–25). According to some authors, the most common finding after the extraction of third molars (16) might be females perceiving more severe post-surgical pain or prolonged recovery (1, 3, 5, 9, 15, 22). Females might be more sensitive to pain stimuli, probably due to reasons such as familial factors, catastrophising, sex hormones and psychosocial factors (16, 24, 25). Nevertheless, in the current study

as well as some other ones (2, 16, 26–29), no such an influence was observed. Even Grossi *et al.* (16). exhibited that although women tended to complain more than men about 'post-surgical sickness, appearance, speech, and eating', their complaints about pain and sensation (and their analgesic consumption) were similar to those of men. Moreover, in another study, it was men who subjectively felt greater pains (although the number of analgesics taken did not differ again) (2). A reason for the greater pain perceived by females in some studies (1, 9, 15) might be the probable higher risk of dry socket formation in females (15), which had not been controlled for in those studies. Furthermore, the effect of gender on post-procedural pain might appear or intensify in adolescence (30). This might contribute to the lack of significant differences in samples with younger patients.

It is suggested that ageing might intensify pain due to factors such as increased bone density (9, 15, 16, 18, 31), completion of root formation and reduced wound healing potential (3). Many authors identified a positive link between age and pain (1, 2, 26, 32). Nevertheless, several other researchers found no pain-related role of age (2, 9, 16–18, 33). Capuzzi *et al.* (2). asserted that younger patients might subjectively report less severe pain, while consuming analgesic doses similar to doses taken by older patients. Another study found more intense pains in younger subjects (3). The present study did not detect a significant association with age. Perhaps, the significant associations observed in the previous research were partly attributable to factors that change with ageing, not necessarily ageing itself. For instance, in case, we had not controlled for the variables 'gender, smoking and the surgical difficulty' in our regression model, age would become significant ($P = 0{\cdot}037$). However, it is noteworthy that the role of age was still marginally significant in the current set-up, even adjusting for the above-mentioned variables. Besides, it should be taken into account that all our patients were in their youth. Probably, by including a larger sample of older people, some direct associations might be observed. The current marginally significant result cannot verify the role of age; and future studies are warranted.

Dry socket pain might be caused by the formation of plasmin in the alveolus. Plasmin can convert kallikrein into kinins and cause neuralgic pain and clot disintegration (6, 7, 10). As dry socket might highly affect pain (15) and confound the results, we also accounted for its effect, for the first time in the literature, while assessing the risk factors of pain. It was interesting that cases diagnosed as dry socket were more painful at both sessions and not just in the third day.

Dry socket pain is unlikely associated with the habitual pain observed post-operatively (21). The pattern of pain reduction differed between dry sockets and intact sockets in this sample, as expected (4–14). The pain of dry sockets perceived at the third post-operative day was higher than normal sockets. However, it was lower than the initial pain felt in the same sockets in the first day. This contradicted the anticipation of a pain that increases in the third day (6, 7, 10–14). However, not knowing the pain levels in the second day, it is not possible to rule out an increase in the third day. Moreover, routine clinical patients mask their pain by taking analgesics in the first few days; subsequently, when they anticipate a lower pain in the next days, an increase might be sensed because of dry socket. Thus, the lack of analgesic consumption might be another factor contributing to the higher pains sensed in the first day, even in dry sockets. Future studies with longer timeframes and more intervals should evaluate this item.

Limitations and strengths

Some limitations constrained this study. A larger sample could favour the reliability of the result. However, power calculations revealed sufficient powers, possibly due to excluding many confounders by the split-mouth design.

The dressing contains 0·5 mg colloidal silver, which allows for a continuous release of silver ions and a subsequent continuous antimicrobial effect. This could act as a confounder. Therefore, cleaner designs (with inert dressings) are definitely necessary to confirm our findings. However, this specific dressing was placed in 'both' the contralateral sockets, and thus, the design remained balanced. Moreover, the CHX application might partly hinder the release of silver ion from the dressing placed in the experimental side. Therefore, if the silver release had any confounding effect, it might favour the pain reduction on the placebo side more than on the CHX side.

Another issue was the subjective nature of pain, which could be affected greatly by cultural and demographic differences, and was difficult to assess

(7, 15). Unlike all previous studies, we did not count systemic analgesic pills consumed, as counting them would reflect the total/maximum pain sensed by each *patient*, not the pain on each surgical site (7). This would eliminate any contrast between the CHX/placebo sides.

There is a possibility that some patients might have lied about avoiding analgesics. However, it was voluntary, and the dropped out patients would receive routine appropriate post-operative care. Therefore, it seemed unlikely that the volunteered patients had secretly taken painkillers.

Excluding the patients consuming analgesics might skew the generalisability of the results to lower pain levels. Perhaps, the inclusion of all patients regardless of their painkiller usage might help in this regard. Nevertheless, such patients will again perceive milder pain, which this might shift the results.

In this study, many patients disagreed to participate because they did not want to risk their health by avoiding painkiller consumption. Their exclusion might skew the sample to more courageous or psychologically prepared and cooperating patients, but not necessarily to the ones with milder pain. The descriptive statistics denote that some volunteers had tolerated rather severe pain levels without taking analgesics. This might favour the generalisability. Perhaps, some of the four patients who did not attend follow-up had ingested painkillers, but it is not known to us.

Another potential limitation was the assessment of multiple painful spots in each patient. The existence of one painful socket might affect (either reduce or increase) the perceived pain on the other socket, and thus decrease the accuracy. However, such a psychological bias was less likely present in this study, because of the following deductions: if the bias was positive, a fainter pain contrast would be expected between the placebo/CHX sides. However, the test power implied a clear difference. If a negative bias existed, some negative correlations between the pain at the two sides would be expected. However, the correlations were positive. Whereas, it was still possible that some patients had positive bias and few had negative bias. This cannot be ruled out, and there seems no other option to conduct a split-mouth study without this limitation. Besides, the excellent intra-rater agreements between the two sessions of this experiment might imply that the reported pain levels were rather accurate. Future studies might further the precision by recording the pain more than once at each session.

Finally, the sample balance and using multivariable analyses on a split-mouth design might better the reliability. The rather sophisticated statistical analyses specified in this study (hierarchical multilevel models including predictor interactions) were unique to the literature. Such analyses might allow for multiple simultaneous adjustments, which are preferable when modelling a complicated system full of interrelated factors (19).

Conclusions

When controlling for other variables and their interactions, it might be inferred that:

1. Chlorhexidine gel might reduce post-operative pain (regardless of its effect on dry socket and infection), particularly in the third day.
2. Pain of dry socket is more severe than the habitual pain routinely perceived after the surgery.
3. Those sockets that will develop dry socket on the *third* day are more painful, even on the *first* day. Severe pain in the first post-operative day might be indicative of a greater risk of dry socket development. This suggestion needs future studies to be verified.
4. In the absence of analgesic consumption, the post-surgical pain might be greater in the first day compared to the third day, in both dry sockets and healthy sockets. However, the pattern of this decrease differs between the two.
5. More difficult surgeries might be more painful and might need more conservative and cautious operations.
6. Smoking habit and gender are less likely affecting post-operative pain.
7. The role of age was inconclusive. This factor needs future studies with larger samples and broader age ranges.

Acknowledgments

The authors wish to express their sincere gratitude to Dr Naiemeh Khamverdi and Dr Hadiseh Khanzadeh-Alishahi for contributing to the data collection. The ethics of this study were approved under 230-20-9/

373 and 230-23-9/374 numbers. The study was self-funded by the authors. The authors declare that they do not have any conflict of interest.

Authors' contributions

The first author (AH) conceived the evaluation of chlorhexidine effect on dry socket and post-operative pain (as theses published earlier) (7), designed the experiments, performed the patient selection and operations, collected the data and mentored the dissertations (7). The second author (VR) conceptualized the assessment of pain prognostic factors, their interactions, the CHX effect on pain controlling for its effect on dry socket as well as the other hypotheses, by analysing the available data. VR also designed and performed the statistical analyses, specified and optimised the regression models, interpreted the findings, searched the literature and drafted/revised the paper.

References

1. Phillips C, White RP Jr, Shugars DA, Zhou X. Risk factors associated with prolonged recovery and delayed healing after third molar surgery. J Oral Maxillofac Surg. 2003;61:1436–1448.
2. Capuzzi P, Montebugnoli L, Vaccaro MA. Extraction of impacted third molars. A longitudinal prospective study on factors that affect postoperative recovery. Oral Surg Oral Med Oral Pathol. 1994;77:341–343.
3. de Santana-Santos T, de Souza-Santos aA, Martins-Filho PR, da Silva LC, de Oliveira E, Silva ED, Gomes AC. Prediction of postoperative facial swelling, pain and trismus following third molar surgery based on preoperative variables. Med Oral Patol Oral Cir Bucal. 2013;18:e65–e70.
4. Lago-Mendez L, Diniz-Freitas M, Senra-Rivera C, Gude-Sampedro F, Gandara Rey JM, Garcia-Garcia A. Relationships between surgical difficulty and postoperative pain in lower third molar extractions. J Oral Maxillofac Surg. 2007;65:979–983.
5. Bienstock DA, Dodson TB, Perrott DH, Chuang SK. Prognostic factors affecting the duration of disability after third molar removal. J Oral Maxillofac Surg. 2011;69:1272–1277.
6. Cardoso CL, Rodrigues MTV, Ferreira Júnior O, Garlet GP, de Carvalho PSP. Clinical concepts of dry socket. J Oral Maxillofac Surg. 2010;68:1922–1932.
7. Haraji A, Rakhshan V, Khamverdi N, Alishahi HK. Effects of intra-alveolar placement of 0.2% chlorhexidine bioadhesive gel on dry socket incidence and postsurgical pain: a double-blind split-mouth randomized controlled clinical trial. J Orofac Pain. 2013;27:256–262.
8. Larrazabal C, Garcia B, Penarrocha M. Influence of oral hygiene and smoking on pain and swelling after surgical extraction of impacted mandibular third molars. J Oral Maxillofac Surg. 2010;68:43–46.
9. Conrad SM, Blakey GH, Shugars DA, Marciani RD, Phillips C, White RP Jr. Patients' perception of recovery after third molar surgery. J Oral Maxillofac Surg. 1999;57:1288–1294; discussion 95–6.
10. Blum IR. Contemporary views on dry socket (alveolar osteitis): a clinical appraisal of standardization, aetiopathogenesis and management: a critical review. Int J Oral Maxillofac Surg. 2002;31:309–317.
11. Bloomer CR. Alveolar osteitis prevention by immediate placement of medicated packing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90:282–284.
12. Noroozi A-R, Philbert RF. Modern concepts in understanding and management of the "dry socket" syndrome: comprehensive review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:30–35.
13. Caso A, Hung L-K, Beirne OR. Prevention of alveolar osteitis with chlorhexidine: a meta-analytic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:155–159.
14. Kolokythas A, Olech E, Miloro M. Alveolar osteitis: a comprehensive review of concepts and controversies. Int J Dent. 2010;2010:249073.
15. Benediktsdóttir IS, Wenzel A, Petersen JK, Hintze H. Mandibular third molar removal: risk indicators for extended operation time, postoperative pain, and complications. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97:438–446.
16. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Creminelli L, Santoro F. Assessing postoperative discomfort after third molar surgery: a prospective study. J Oral Maxillofac Surg. 2007;65:901–917.
17. Akadiri OA, Okoje VN, Arotiba JT. Identification of risk factors for short-term morbidity in third molar surgery. Odontostomatol Trop. 2008;31:5–10.
18. Baqain ZH, Karaky AA, Sawair F, Khraisat A, Khaisat A, Duaibis R *et al.* Frequency estimates and risk factors for postoperative morbidity after third molar removal: a prospective cohort study. J Oral Maxillofac Surg. 2008;66:2276–2283.
19. Haraji A, Rakhshan V. Single-dose intra-alveolar chlorhexidine gel application, easier surgeries, and younger ages are associated with reduced dry socket risk. J Oral Maxillofac Surg. 2014;72:259–265.
20. Pederson GW. Oral surgery. Philadelphia: WB Saunders; 1988.
21. Penarrocha M, Sanchis JM, Saez U, Gay C, Bagan JV. Oral hygiene and postoperative pain after mandibular third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;92:260–264.
22. Yuasa H, Sugiura M. Clinical postoperative findings after removal of impacted mandibular third molars: prediction of postoperative facial swelling and pain based on preoperative variables. Br J Oral Maxillofac Surg. 2004;42:209–214.

23. Kazemi M, Geramipanah F, Negahdari R, Rakhshan V. Active tactile sensibility of single-tooth implants versus natural dentition: a split-mouth double-blind randomized clinical trial. Clin Implant Dent Relat Res. 2014;16:947–955.
24. Fillingim RB. Sex, gender, and pain: women and men really are different. Curr Rev Pain. 2000;4:24–30.
25. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000;87:325–334.
26. Fisher SE, Frame JW, Rout PG, McEntegart DJ. Factors affecting the onset and severity of pain following the surgical removal of unilateral impacted mandibular third molar teeth. Br Dent J. 1988;164:351–354.
27. Macgregor AJ, Addy A. Value of penicillin in the prevention of pain, swelling and trismus following the removal of ectopic mandibular third molars. Int J Oral Surg. 1980;9:166–172.
28. Seymour RA, Blair GS, Wyatt FAR. Postoperative dental pain and analgesic efficacy. Part I.. Br J Oral Surg. 1983;21:290–297.
29. Seymour RA, Meechan JG, Blair GS. An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg. 1985;23:410–418.
30. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL III. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain. 2009;10:447–485.
31. Bui CH, Seldin EB, Dodson TB. Types, frequencies, and risk factors for complications after third molar extraction. J Oral Maxillofac Surg. 2003;61:1379–1389.
32. Osborn TP, Frederickson G Jr, Small IA, Torgerson TS. A prospective study of complications related to mandibular third molar surgery. J Oral Maxillofac Surg. 1985;43:767–769.
33. Adeyemo WL, Ogunlewe MO, Ladeinde AL, Hassan OO, Taiwo OA. A comparative study of surgical morbidity associated with mandibular third-molar surgery in young and ageing populations. J Contemp Dent Pract. 2010;11:E001–E008.

Correspondence: Vahid Rakhshan, Department of Dental Anatomy and Morphology, Dental Branch, Islamic Azad University, Tehran, PO Box 19585-175, Iran.
E-mail: v_rakhshan@dentaliau.ac.ir