

# Controlling Orthodontic Pain from Orthodontists Perspectives-A Survey

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## ABSTRACT

**Background:** The aim of this study was to determine the most preferred approach for orthodontic pain control adopted by a sample of Iraqi orthodontists.

**Materials and methods:** An electronic survey using Google Forms was conducted from the 7th of March till the end of April 2021. The survey consisted of three options according to the preferred approach used by Iraqi orthodontists to minimize orthodontic pain. Data were collected and Pearson's chi-squared test was applied to determine the gender difference.

**Results:** The response rate was 70%. More than half of the respondents preferred using both the pharmacological and non-pharmacological approaches. Paracetamol is considered the drug of choice prescribed by the majority of orthodontists, mainly after initial placement of arch wire and used until the pain is resolved.

**Conclusions:** More than half of the respondents rely on using both approaches of pain management. Paracetamol is the drug of choice for alleviating pain and mostly prescribed until the pain is resolved, keeping in mind not exceeding the maximum allowed dose. Psychological perspectives and behavioural management was the preferred method as a non-pharmacological approach.

**Key words:** Pain, Analgesics, Orthodontics, NSAIDs, Drug therapy

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## INTRODUCTION

Pain is considered as one of the major reasons behind why patients hesitate to seek or discontinue orthodontic treatment, with about 30% requesting to prematurely finish treatment as a result [1]. It can be defined as an obnoxious sensory experience accompanied with actual or potential tissue damage or is expressed in terms of such damage. Like any pain, orthodontic pain is perceived as discomfort, dull pain and hypersensitivity in affected teeth [2-3].

The real mechanism of orthodontic pain is not fully understood, yet several theories have attempted to explain it. It has been proposed that exerting orthodontic force will lead to the development of pressure, ischemia, inflammation and oedema, which will in turn cause periodontal pain [4]. This inflammatory process will be accompanied by an increase in the number of multinuclear osteoclasts and promote osteoclastic bone resorption that allows tooth movement, and additionally, the release of high levels of prostaglandins, histamine, serotonin,

bradykinin, substance P and cAMP to the periodontal ligament [5].

There is a general agreement that orthodontic pain starts two to four hours after the application of orthodontic force reaching its peak after 24 hours and lasting about five days [6].

Orthodontic pain may arise after different procedures, such as after the placement of separators and initial arch wire, miniscrew anchorage, debonding, rapid maxillary expansion and so on [7].

Many methods have been developed to manage orthodontic pain [8]. A number have depended on pharmacological approaches and the others, on non-pharmacological approaches. Pharmacological approaches use analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, thus relieving orthodontic pain. The side effects of these drugs include gastro-intestinal upsets and are therefore unsuitable for patients with digestive tract problems; additionally, they delay orthodontic tooth movement as they interfere with collagenase activity and procollagen synthesis, resulting in impeded periodontal remodelling [9].

Non-pharmacological approaches for patients include chewing gum, biting on wafers and receiving are assuring

telephone call from their doctor or specialist. The behavioural approach, low-level laser therapy, vibration and gene therapy are all used for pain control, yet the quality of evidence supporting these methods is low [10].

No survey of orthodontists' opinions about the methods of orthodontic pain management has ever been undertaken. Therefore, this study was conducted to ascertain orthodontic pain management approaches that are most commonly used by Iraqi orthodontists.

### MATERIAL AND METHOD

Firstly, the approval of the scientific committee in the College of Dentistry, the University of Baghdad was gained to conduct this cross-sectional online survey.

A survey on Google Forms was prepared and consisted of three sections, each respectively dedicated to the approaches used by orthodontists in managing orthodontic pain, namely: non-pharmacological approaches, pharmacological approaches and both approaches.

This form was validated by ten orthodontists then distributed to the active members of the Iraqi Orthodontic Society via e-mail, the Telegram channel of Iraqi orthodontists and the Facebook page of Iraqi orthodontists. About 230 Iraqi orthodontists were invited to participate in this questionnaire to answer the following questions:

#### Gender: Male, Female

How did you manage orthodontic pain of your patients?

- a) Non-pharmacological
- b) Pharmacological
- c) Both

#### Regarding the non-pharmacological approach

Which method you prescribed? (You can choose more than one method)

- a) Chewing gum
- b) Biting on wafer
- c) Vibration
- d) Systemic acupuncture
- e) Psychological perspective and behavioral management
- f) Low level laser therapy
- g) Telephone call

#### Regarding the pharmacological approach

Which drugs you prescribed? (You can choose more than one drug)

- a) Paracetamol
- b) Ibuprofen
- c) Ponstan

- d) Voltaren
- e) Aspirin
- f) Naproxen
- g) Feldene
- h) Mobic

What is the dose you prescribed?

- a) Once daily
- b) Twice daily
- c) Three times daily
- d) On need but not exceeding the maximum limit

What is the form you prescribed?

- a) Tablets/ capsules
- b) Sachet
- c) Injection
- d) Suppository

Did you ask the patients about any history of hypersensitivity for the prescribed analgesics?

- a) Yes
- b) No
- c) Sometimes

Did you ask the patients about taking medication that may interact with the prescribed analgesics?

- d) Yes
- e) No
- f) Sometimes

When did you prescribe analgesic?

- a) After separator placement
- b) After bonding and initial arch wire placement
- c) After activation using power chain/ closed coil or closing loops or using inter-maxillary elastics
- d) Each visit involves arch wire changing
- e) All of the above

How long should patients take analgesics?

- a) Just one day
- b) Two days
- c) Three days
- d) One week
- e) Till pain resolved

What is the best approach to minimize orthodontic pain for pregnant women?

- a) Consult gynaecologist
- b) I do not prescribe any drug

- c) Non-pharmacological approach
- d) Prescribing Paracetamol

#### Regarding both approaches

Which drugs you prescribed? (You can choose more than one drug)?

- a) Paracetamol
- b) Ibuprofen
- c) Ponstan
- d) Voltaren
- e) Aspirin
- f) Naproxen
- g) Feldene
- h) Mobic

What is the dose you prescribed?

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- b) Twice daily
- c) Three times daily
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What is the form you prescribed?

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Did you ask the patients about any history of hypersensitivity for the prescribed analgesics?

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- e) Till pain resolved

What is the best approach to minimize orthodontic pain for pregnant women?

- a) Consult gynaecologist
- b) I do not prescribe any drug
- c) Non-pharmacological approach
- d) Prescribing Paracetamol

#### Statistical analyses

Data were collected and analysed by SPSS program (version 25). Frequency tables and gender differences were calculated by Pearson's Chi-square test with a 0.05 probability level.

#### RESULTS

About 230 Iraqi orthodontists were invited to participate in this survey. Only 161 participated, bringing the response rate to 70%.

Table 1 provides a presentation of the distribution of responses according to the approach of managing orthodontic pain and genders. The respective breakdown of male to female participation was 46% to 54%. With respect to the approach used, 14% preferred the non-pharmacological approach with an equal split in genders. Meanwhile 30% used the pharmacological approach with a slightly higher number of females favouring this approach (52%). However, more than half of the participants (57%) preferred to use both approaches, with more females favouring both approaches (56%).

With regard to the non-pharmacological approach, 45% of the respondents preferred using psychological perspectives and behavioural management, and of this, 55% were males and 36% were females. Other methods such as biting on wafers, chewing gum or telephone calls were used by fewer participants as the only method for pain management. About 36% used more than one method, with statistically no significant gender difference (Table 2).

Table 3 outlined the responses of orthodontists using the pharmacological approach. To manage orthodontic pain, Paracetamol was the drug of choice for 73% of the participants (70% of males and 76% of females). Other drugs like Ibuprofen and Mefenamic acid were rarely used. About 23% preferred to use more than one drug from the list, of them 22% were males and 24% were females. The chi-squared test revealed a non-significant gender difference.

With regards to the frequency of drug intake, 85% of orthodontists instructed their patients to take the drug as required but to not exceed the allowable daily limit. About 13% of males prescribed analgesics three times

daily. The difference between males and females was non-significant. Interestingly, all orthodontists prescribed analgesics in the form of tablets or capsules.

The majority of the participants took the history about allergy to analgesics and any possibility of drugs interference (63% and 48% respectively) with no gender differences.

About 65% males and 36% females preferred to prescribe analgesics after bonding and initial archwire placement; yet 31% prescribed analgesics after every orthodontic procedure expecting it would cause pain. Again, no gender difference was reported.

With respect to the duration of analgesic use, 44% instructed their patients to take analgesics until the pain was resolved, while 40% prescribed the drugs for two to three days with no significant gender difference.

Paracetamol was prescribed by 48% of respondents to manage orthodontic pain in pregnant women. About 19% did not prescribe drugs and 17% preferred to consult the gynaecologist or used the non-pharmacological approach, again, with a non-significant gender difference.

**Table 1: Distribution of participants according to the genders and approached used to manage orthodontic pain.**

Genders	Approach of orthodontic pain relieve							
	Non-Pharmacological		Pharmacologica l		Both		Total	
	N	%	N	%	N	%	N	%
Males	11	50	23	48	40	44	74	46
Females	11	50	25	52	51	56	87	54
Total	22	13	48	30	91	57	161	100

**Table 2: Frequency distributions and gender difference of responses preferred the non-pharmacological approach.**

Non-Pharmacologica l approach	Males		Females		Total		Gender Difference	
	N	%	N	%	N	%	X2	p-value
Biting on wafer	0	0	1	9	1	5	4.4	0.355
Chewing gum	0	0	2	18	2	9		
Psychological perspective and behavioral management	6	55	4	36	10	45		
Telephone call	1	9	0	0	1	5		
Combination of any methods	4	36	4	36	8	36		
Total	11	100	11	100	22	100		

**Table 3: Frequency distributions gender difference of responses the preferred pharmacological approach**

Pharmacological approach		Males		Females		Total		Gender difference	
		N	%	N	%	N	%	X2	p-value
Drugs used to relieve orthodontic pain	Acetaminophe n (Paracetamol or Panadol)	16	70	19	76	35	73	2.269	0.518
	Ibuprofen (Profen)	1	4	0	0	1	2		
	Mefenamic acid (Ponstan)	1	4	0	0	1	2		
	More than one drug	5	22	6	24	11	23		
Total	23	100	25	100	48	100			

<b>Frequency of intake</b>	On need but not exceeding the daily allowed limit	17	74	24	96	41	85	5.455	0.141
	Once daily	1	4	0	0	1	2		
	Three times daily	3	13	0	0	3	6		
	Twice daily	2	9	1	4	3	6		
	Total	23	100	25	100	48	100		
	Tablet/Capsule	23	100	25	100	48	100	-	-
	Injection	0	0	0	0	0	0		
	Sachet	0	0	0	0	0	0		
	Suppository	0	0	0	0	0	0		
	Total	23	100	25	100	48	100		
<b>Inquiry about the history of hypersensitivity to any analgesics</b>	No	4	17	2	8	6	13	1.119	0.571
	Sometime	6	26	6	24	12	25		
	Yes	13	57	17	68	30	63		
	Total	23	100	25	100	48	100		
<b>Inquiry about any medication that may interfere with analgesics</b>	No	7	30	2	8	9	19	4.038	0.133
	Sometime	7	30	9	36	16	33		
	Yes	9	39	14	56	23	48		
	Total	23	100	25	100	48	100		
<b>Cases that analgesics will be prescribed</b>	After activation using power chain/ closed coil or	0	0	4	16	4	8	8.031	0.09
	closing loops or using inter-maxillary elastics								
	After bonding and initial archwire placement	15	65	9	36	24	50		
	After separator placement	1	4	3	12	4	8		
	Each visit involve archwire changing	1	4	0	0	1	2		
	All of the above	6	26	9	36	15	31		
	Total	23	100	25	100	48	100		
<b>Duration of taking analgesics</b>	Just one day	3	13	4	16	7	15	1.543	0.672
	One week	1	4	0	0	1	2		
	Till the pain resolved	9	39	12	48	21	44		
	Two- three days	10	43	9	36	19	40		
	Total	23	100	25	100	48	100		
<b>The best approach to manage</b>	Consult gynecologist	3	13	5	20	8	17	2.924	0.403

orthodontic pain in pregnant women	I do not prescribe any drug	4	17	5	20	9	19
	Non-pharmacological approach	6	26	2	8	8	17
	Prescribing Paracetamol	10	43	13	52	23	48
	Total	23	100	25	100	48	100

Table 4 demonstrated the responses of orthodontists using both approaches. For the non-pharmacological approach, 32% preferred applying psychological perspectives and behavioural management while 12% prescribed chewing gum, 10% made telephone calls and 44% used more than one method. A chi-squared test revealed a statistically significant gender difference.

Regarding the medication used to manage orthodontic pain, Paracetamol was the drug of choice for 64% of the participants (58% of males and 69% of females). Other drugs such as Ibuprofen, Mefenamic acid and Diclofenac sodium were rarely used. About 29% preferred to use more than one drug from the list, and of them, 40% were males and 22% were females. The gender difference was not significant.

With regards to the frequency of drug intake, 68% of the orthodontists instructed their patients to take the drug as required but not to exceeding the allowable daily limit. The difference between male and female responses was highly significant. All orthodontists prescribed the analgesics in the form of tablets or capsules.

The majority of the participants took the history about allergy to analgesics and any possibility of drugs interference 65% and 68% respectively with no gender differences.

Just like in the pharmacological approach, about 50% males and 47% females preferred to prescribe analgesics after bonding and initial arch wire placement; moreover, 24% prescribed analgesics after every orthodontic procedure expecting it would cause pain. Again, no gender difference was reported.

With respect to the duration of analgesic use, 35% instructed their patients to take analgesics until the pain was resolved, while 45% prescribed the drugs for two to three days, with no significant gender difference.

To manage orthodontic pain in pregnant women, Paracetamol was prescribed by 36% of respondents. About 12% did not prescribe drugs, 22% preferred to consult the gynaecologist and 30% used the non-pharmacological approach with a highly significant gender difference.

**Table 4: Frequency distributions and gender difference of responses preferred both approaches**

Both Approaches		Males		Females		Total		Gender difference	
		N	%	N	%	N	%	X2	p-value
Non-pharmacological approach	Biting on wafer	1	3	1	2	2	2	13.533	0.009
	Chewing gum	9	23	2	4	11	12		
	Psychological perspective and behavioral management	13	33	16	31	29	32		
	Telephone call	0	0	9	18	9	10		
	More than one method	17	43	23	45	40	44		
	Total	40	100	51	100	91	100		
Drugs used to relieve orthodontic pain	Acetaminophen (Paracetamol or Panadol)	23	58	35	69	58	64	5.493	0.24
	Diclofenac sodium (Voltaren)	0	0	1	2	1	1		
	Ibuprofen (Profen)	0	0	2	4	2	2		

	Mefenamic acid (Ponstan)	1	3	2	4	3	3		
	More than one drug	16	40	11	22	26	29		
	Total	40	100	51	100	91	100		
<b>Frequency of intake</b>	On need but not exceeding the daily allowed limit	22	55	40	78	62	68	12.658	0.005
	Once daily	3	8	5	10	8	9		
	Three times daily	8	20	0	0	8	9		
	Twice daily	7	18	6	12	13	14		
	Total	40	100	51	100	91	100		
<b>Route of intake</b>	Tablet/ Capsules	40	100	51	100	91	100	-	-
	Injection	0	0	0	0	0	0		
	Sachet	0	0	0	0	0	0		
	Suppository	0	0	0	0	0	0		
	Total	40	100	51	100	91	100		
<b>Inquiry about the history of hypersensitivity to any analgesics</b>	No	6	15	6	12	12	13	0.732	0.694
	Sometime	10	25	10	20	20	22		
	Yes	24	60	35	69	59	65		
	Total	40	100	51	100	91	100		
<b>Inquiry about any medication that may interfere with analgesics</b>	No	6	15	8	16	14	15	0.139	0.932
	Sometime	6	15	9	18	15	16		
	Yes	28	70	34	67	62	68		
	Total	40	100	51	100	91	100		
<b>Cases that analgesics will be prescribed</b>	After activation using power chain/ closed coil	3	8	7	14	10	11	5.363	0.252
	or closing loops or using inter-maxillary elastics								
	After bonding and initial archwire placement	20	50	24	47	44	48		
	After separator placement	4	10	9	18	13	14		
	Each visit involve archwire changing	0	0	2	4	2	2		
	All of the above	13	33	9	18	22	24		
	Total	40	100	51	100	91	100		
<b>Duration of taking analgesics</b>	Just one day	4	10	10	20	14	15	1.879	0.598
	One week	2	5	2	4	4	4		
	Till the pain resolved	16	40	16	31	32	35		

	Two- three days	18	45	23	45	41	45		
	Total	40	100	51	100	91	100		
<b>The best approach to manage orthodontic pain in pregnant women</b>	Consult gynecologist	9	23	11	22	20	22	11.862	0.008
	I do not prescribe any drug	1	3	10	20	11	12		
	Non-pharmacological approach	9	23	18	35	27	30		
	Prescribing Paracetamol	21	53	12	24	33	36		
	Total	40	100	51	100	91	100		

**DISCUSSION**

In the past few years, an increasing demand for as less as painful orthodontic treatment has been raised. No matter, orthodontic treatment will be accompanied by pain that differed among individuals and related to the pain threshold, type of malocclusion and appliance used.

To the authors' knowledge, no previous study has been conducted from the perspective of orthodontists in regard to the type of pain-relieving medications being prescribed, as previous research efforts only studied the patients' opinions on this topic. Therefore, the current study has been conducted. In regard to pain associated with anchorage devices, extra-oral traction methods or rapid maxillary expansion, the author preferred to exclude them as not all Iraqi orthodontists used these strategies in daily practice.

Generally, the results will be discussed in three parts according to the preferred method used by Iraqi orthodontists for pain relief.

**Orthodontic pain relief by non-pharmacological approach**

According to the Cochrane review published by Fleming et al. [10] in 2016, the quality of evidence supporting the use of non-pharmacological approaches for managing orthodontic pain was very low. Nevertheless, about 13% of participants preferred the use of non-pharmacological approaches with equal gender distributions (Table 1).

Table 2 shows that about 45% of respondents used behavioural management, underpinned by psychological perspectives, as a major method for pain relief. However, 36% of the participants preferred to use more than one method like prescribing the chewing of gum, making telephone calls and applying psychological perspectives and behavioural management, with no gender difference. One female orthodontist prescribed biting on wafers.

Many orthodontists preferred applying psychological perspectives and behavioural management by establishing a good orthodontist-patient rapport, explaining the mechanism of orthodontic pain, especially after the placements of separator and arch wire, and reassuring the patients about the pain [11].

It has been proposed that chewing gum and biting wafers activate the mechanoreceptors which transmit tactile signals, and thus, suppressing the transmission of painful signals; additionally, this method accelerates blood flow into and around the periodontal ligament (PDL), and hence reduces the edema produced by the trauma of orthodontic forces [12]. Chewing gum must be used with caution to minimize the possibility of bracket debonding.

Regarding using a telephone call to follow-up, Cozzani et al. [13] concluded that telephone call follow ups might effectively alleviate the pain threshold of orthodontic patients. This method looks more appropriate during the COVID-19 pandemic and lockdown periods.

**Orthodontic pain relief by pharmacological approaches**

According to the observations in Table 1, 35% of participants preferred the pharmacological approach. The drug of choice used to relieve orthodontic pain was Paracetamol as it had no gastro-intestinal tract toxicity and had no impeding effect on orthodontic tooth movement because it inhibited the peripheral prostaglandin E synthesis at the level of the periodontal ligament.

Krasny et al. [14] stated that Paracetamol is the drug of choice for orthodontic pain alleviation as its action is comparable to the most efficient analgesics with fewer side effects. The findings of a study by Krasny et al. [14] supported that of the current study, as 73% of the participants prescribed Paracetamol as the first-line drug.

Other drugs such as Ibuprofen and Mefenamic acid were used less often due to their side effect on the gastro-intestinal tract or tooth movement. About 23% preferred to use more than one drugs according to the patients' response, sensitivity and/or the presence of drug interference. No gender difference was reported regarding the type of medications prescribed.

Regarding the frequency of drug intake, 85% instructed their patients to take pain killers as required but not exceeding the allowable daily limit, as the patients differed in their pain threshold, type of malocclusion,

type of orthodontic appliance and arch wire used. About 6% were prescribed painkillers twice or thrice per day to prevent drug abuse or the risk of overdose, and these strict instructions were considered safer than the first choice. Again, no statistical gender difference was observed.

Participants appeared to generally agree that drug intake by oral means was safer, quicker and did not cause trauma or irritation like that caused by rectal or intramuscular injection. Painkillers in sachet form were available but were not prescribed by any orthodontists.

Asking patients about hypersensitivity or seeking information about drug interference was a very important issue. The majority of participants confirmed this subject, with no gender difference. Less than 20% did not ask their patients about drug hypersensitivity and whether patients took other medication that might interfere with the prescribed analgesics. This is dangerous for the patients and not acceptable from a medico-legal point of view.

Fifty percent of participants prescribed analgesics to reduce orthodontic pain after bonding and initial wire placement, as pain tended to start after 2–4 hours and reached the peak after 24 hours [6, 15]. About 8% prescribed painkillers after the placement of elastic separators and after activation using power chain/ NiTi closed coil, closing loops or using inter-maxillary elastics. On the other hand, 31% prescribed analgesics after all these procedures with no statistically significant gender difference. With the development of direct bonding and bondable molar tubes, the need for the placement of orthodontic bands was reduced and became restricted to cases which required the inclusion of quadhelix, transpalatal bar or Hyrax expanders.

Many studies have documented that orthodontic pain begins 2–4 hours after applying orthodontic force reaching a peak after 24 hours, and lasting 2–3 days, and then diminishing little by little by the fifth or sixth days, before returning to baseline levels after one month [6]. According to this finding, 44% and 40% of the participants prescribed analgesics until the pain resolved or for 2–3 days respectively. About 15% instructed their patients to use painkillers for just one day, while only 2% for one week, with no significant gender difference.

To relieve orthodontic pain in pregnant women, 48% prescribed Paracetamol, 19% did not prescribed any painkiller and 17% preferred to consult the gynecologist or used the non-pharmacological approach with no gender difference. Paracetamol was the drug of choice used during pregnancy [16] as NSAIDs may have a deleterious effect on the embryo; additionally, Paracetamol does not cross the placenta, although some studies reported a number of problems such as attention-deficit hyperactivity, autism and asthma [17,18]. In a recent epidemiological study, Bandoli et al. [16] reported that 65% of pregnant women used Paracetamol to control pain, supporting the findings of the current study. Nevertheless, the information about whether it is safe to use Paracetamol during pregnancy is inadequate. To

remain on the safe side, gynaecologist must be consulted to avoid risks of drug interference or about the side effects of analgesics according to the trimester.

### Orthodontic pain relief by both approaches

Table 1 showed that 57% of the participants preferred both approaches. For the non-pharmacological approach, 32% used behavioural management, underpinned by psychology, as a main method for pain relief. Biting on wafers or chewing gum was also used, but by fewer participants. Telephone calls were observed to be used mainly by females as most of the orthodontic patients were females and females could communicate easily together by phone.

In 44% of the responses, orthodontists preferred using more than one method, i.e., a combination of two or three methods, as this approach was related to a good relationship between the orthodontists and their patients, in addition to confidence of the efficacy of non-pharmacological methods in reducing orthodontic pain. Statistically, Pearson's chi-squared test revealed a significantly high gender difference (Table 4).

Similar to responses about the pharmacological approaches, Paracetamol was the drug of choice in alleviating pain. About 29% used more than one drug according the pain threshold and stage of treatment. Again, respondents prescribed analgesics as required but not exceeding the allowable daily limit and asked patients about their history of drug hypersensitivity and the possibility of interaction, with no gender difference (Table 4).

The main situation in which orthodontists prescribed analgesics to relief pain was after bonding and initial archwire placement. A low percentage of responses were observed against the cases of separator placement or the activation of the closing loop or coil. On the other hand, 24% prescribed analgesics in all above situations.

Thirty five percent of orthodontists instructed their patients to take analgesics until the pain was resolved while 45% instructed them to take the medication for 2–3 days, as pain started after 2-4 hours from applying orthodontic force and reached the maximum after one day, and lasted for 2–3 days before diminishing [6].

Similar to the responses in pharmacological approaches, 36% of the respondents prescribed Paracetamol and used 30% used non-pharmacological approaches to manage the pain in pregnant orthodontic patients; on the other hand, 22% preferred gynaecologist consultation before prescribing any analgesics.

### CONCLUSIONS

As a conclusion, more than half of the respondents rely on using both approaches of pain management. Paracetamol was the drug of choice for alleviating pain and mostly prescribed till pain resolved keeping in mind not exceeding the maximum allowed dose. Psychological perspectives and behavioural management was the preferred method as a non-pharmacological approach.

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