

# Onset of Action and Efficacy of Ibuprofen Liquigel as Compared to Solid Tablets: A Systematic Review and Meta-Analysis

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**ABSTRACT. Purpose.** Ibuprofen liquigel has been believed to provide faster analgesic effect. However, comparative studies evaluating the efficacy of liquigel versus regular tablets are not available. Hence, we carried out a systematic review and a meta-analysis to compare the onset of action and efficacy of over-the-counter doses of ibuprofen liquigel (IBU<sub>LG</sub>) vs ibuprofen tablets (IBU<sub>T</sub>). **Methods.** Published clinical trials of IBU<sub>LG</sub> and IBU<sub>T</sub> were identified through a systematic search of various data bases up to October, 2015. **Results.** In total 18 eligible studies on IBU<sub>T</sub> and 4 on IBU<sub>LG</sub> were found. There was no significant difference in the median time to the first perceptible pain relief or the proportion of patients with more than 50% pain relief between the two products. However, IBU<sub>LG</sub> yielded significantly greater odd ratios in meaningful pain relief at 60, 90 and 120 min, but not at 30 min, as compared with IBU<sub>T</sub>. **Conclusion.** The available evidence, although not overwhelming, suggest a faster onset of analgesia for liquigel as compared with tablets.

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## INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) derivative of the propionic acid that is used throughout the world for relief of pain and inflammation in both acute and chronic conditions [1]. The favorable analgesic effect of ibuprofen, even at low over-the-counter (OTC) oral doses, has made this agent the gold standard against which many new agents are evaluated for efficacy [2].

The management of acute episodes of pain requires the use of analgesic agents that have the ability to get absorbed rapidly and efficiently to yield rapid onset of pain relief. Ibuprofen is a Biopharmaceutics Classification System (BCS) ([3]) class II drug with low solubility at pH 1.2 and 4.5 but high solubility at pH 6.8, and is very permeable through physiological membranes [4]. In fact, it is found to be completely absorbed allowing for almost total bioavailability. However, the onset of absorption greatly depends on the dissolution of the dosage form [5].

In recent years, various oral formulations and different salts of ibuprofen have been investigated for their absorption properties and for their speed of onset of action with the hope of providing a rapid rise in plasma concentrations and, hence, a fast analgesic effect. They include S(+) ibuprofen [6],

ibuprofen lysine [7, 8], ibuprofen sodium [9], ibuprofen arginate [7, 10], and ibuprofen liquigel (Advil Liqui-Gels, Pfizer, NY, USA).

Ibuprofen liquigel is a soft gelatin capsule that is hermetically sealed and contains ibuprofen as free acid and potassium salt in a solubilised form [11]. This newer solid dosage form of ibuprofen has been reported to have a rapid rate of absorption in healthy volunteers [12]. While ibuprofen rate of absorption in patients in pain is not reported, it has been shown to be an effective analgesic with minor advantages in onset of action as compared with ketoprofen and acetaminophen 1000 mg [13, 14]. However, results of clinical trials, if any, that compare liquigel with solid dosage forms of ibuprofen as an active comparator have not been reported, hence, any advantage of such formulations remains unproven. This is particularly important since, due to the popularity of ibuprofen liquigel, many other analgesics have become available on the market in the form of liquid gel. We, therefore, attempted to compare the onset of analgesia and efficacy of the liquigel with solid dosage forms of ibuprofen by

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undertaking a systematic review and meta-analysis of all the studies that report onset of analgesia and efficacy of ibuprofen after administration of these formulations for the treatment of dental pain or migraine or tension-type headache.

## METHOD

Published reports of randomized controlled trials on ibuprofen tablets (IBU<sub>T</sub>) or liquisol (IBU<sub>LG</sub>) at any dose were identified through a systematic search of PubMed, Embase, Google Scholar and the Cochrane library from inception until October, 2015. Key words used in the search included: ibuprofen, onset, human, dental, oral surgery, migraine, and tension-type headache. Moreover, the reference lists of the retrieved articles were scanned for relevant studies. The screening and eligibility assessment of the reports was carried out independently by the two authors. There was a lack of access to unpublished data, and so the review only included published reports. Moreover, conference abstracts, case reports, or clinical observations were found to lack the details required in the analysis, and thus were not included. No language restriction was imposed.

The review was restricted to clinical studies related to the use of ibuprofen as an analgesic for dental pain, tension-type headache, and migraine. Studies were included if they were randomized, double blind, and placebo controlled studies that evaluated a single dose of ibuprofen administered following a moderate to severe episode of pain associated with one of the above mentioned conditions. Multiple dose studies were included only if the relevant single-dose data were provided. Studies on the use of ibuprofen as a pre-emptive treatment were not included, nor were studies which only used other than the conventional marketed IBU<sub>T</sub> or IBU<sub>LG</sub>. Therefore, ibuprofen salt formulations marketed such as ibuprofen sodium or ibuprofen arginate were excluded from the review. The inclusion criteria also required the use of the double stopwatch method, a patient population aged at least 12 years, and monitoring the patients for three hours or more post-dose.

Relevant studies were categorised on the basis of whether the ibuprofen solid tablets or the ibuprofen liquisol were used. In instances where the results from the studies were only reported graphically, the relevant graphs were digitized using digitizeit (<http://www.digitizeit.de>, Germany) and the "grabit" function in MATLAB (MathWorks Inc., Natick MA,

USA), and the data were extracted. In particular, the Kaplan-Meier time to event curves were analysed by the approach suggested by Guyot et al [15].

Two measures of onset of pain relief were considered, namely, the time to the first perceptible pain relief (FPPR) and the meaningful pain relief (MPR), both of which are patient-reported outcome captured as part of the double stopwatch method [16]. Kaplan-Meier survival median times to the above events were averaged with the weights being proportional to both the sample sizes and inverse of the variance. The latter, however, was measurable only for the data reported in the studies that provided a measure of variance. Moreover, the outcome of achieving meaningful pain relief at 30, 60, 90, and 120 min post-dose were calculated. The proportion of patients achieving MPR at the above specific times, and the relevant odd ratios (OR) against placebo were calculated. Setting IBU<sub>T</sub> as the reference (OR=1), the OR for IBU<sub>LG</sub> was also calculated by an adjusted indirect comparison [17]. Variation among studies was anticipated, and due to the heterogeneity of the pooled data the OR values for meaningful pain relief were estimated using the DerSimonian-Laird method [18]. Heterogeneity among the studies in reporting an outcome is detected using the Cochran-Q test and the percentage of variation across the different studies that is attributed to heterogeneity is quantified using the I<sup>2</sup> inconsistency test.

As the measure of efficacy, we calculated the total pain relief score (TOTPAR) over 6 h. Pain relief is measured throughout the study at specific time intervals on a 5-point categorical scale (0 (no relief), 1 (slight relief), 2 (moderate relief), 3 (good relief), 4 (complete relief)). TOTPAR, which is an integrated pain score representing a time-weighted measure of the total area under the pain relief curve, has a higher sensitivity than many other outcome measures such as the sum of pain intensity difference score [19]. We used the Student's t-distribution test to compare the calculated TOTPAR scores [20]. Moreover, we used verified linear regression equations to calculate the proportion of patients experiencing more than 50% pain relief as measured by TOTPAR, and calculated the relevant ORs against placebo and against each other [21].

## RESULTS

The database search (Figure 1) resulted in 100 reports that evaluated ibuprofen treatment for dental

pain or dental surgery, migraine, or headache, and 3 additional reports were identified from other resources.

Upon our preliminary screening, duplicate reports, only abstracts, case studies, reviews and observational studies were removed. Subsequently, the list was shortened to 64 reports. A further screening revealed that 12 of these reports did not use randomly controlled trials, and 10 did not include ibuprofen as an active comparator in the study; e.g., as a rescue medication. The remaining 42 full text articles were checked for eligibility. Among these, 4 studies were related to the use of ibuprofen as a pre-emptive treatment, 2 used ibuprofen lysine, 1 used extended-release ibuprofen, 1 used sodium ibuprofen

and ibuprofen acid incorporating poloxamer, 8 did not include results of the double stopwatch method, 3 were not placebo-controlled studies, and 1 did not report placebo results. The remaining 22 studies (Table 1) met our inclusion criteria and were included in the review. These consisted of 18 studies that used IBU<sub>T</sub> and 4 that studied IBU<sub>LG</sub>. Among the IBU<sub>T</sub> studies, 4 used Motrin IB (Motrin, McNeil Consumer Healthcare, Fort Washington PA, USA) (IBU<sub>Mot</sub>), one used Advil (Pfizer Consumer Healthcare, New York NY, USA), one had an arm for each of these two brands, one used Neurofen (Reckitt Benckiser, Slough, UK), while the rest either used unbranded ibuprofen tablets or did not specify the brand used.

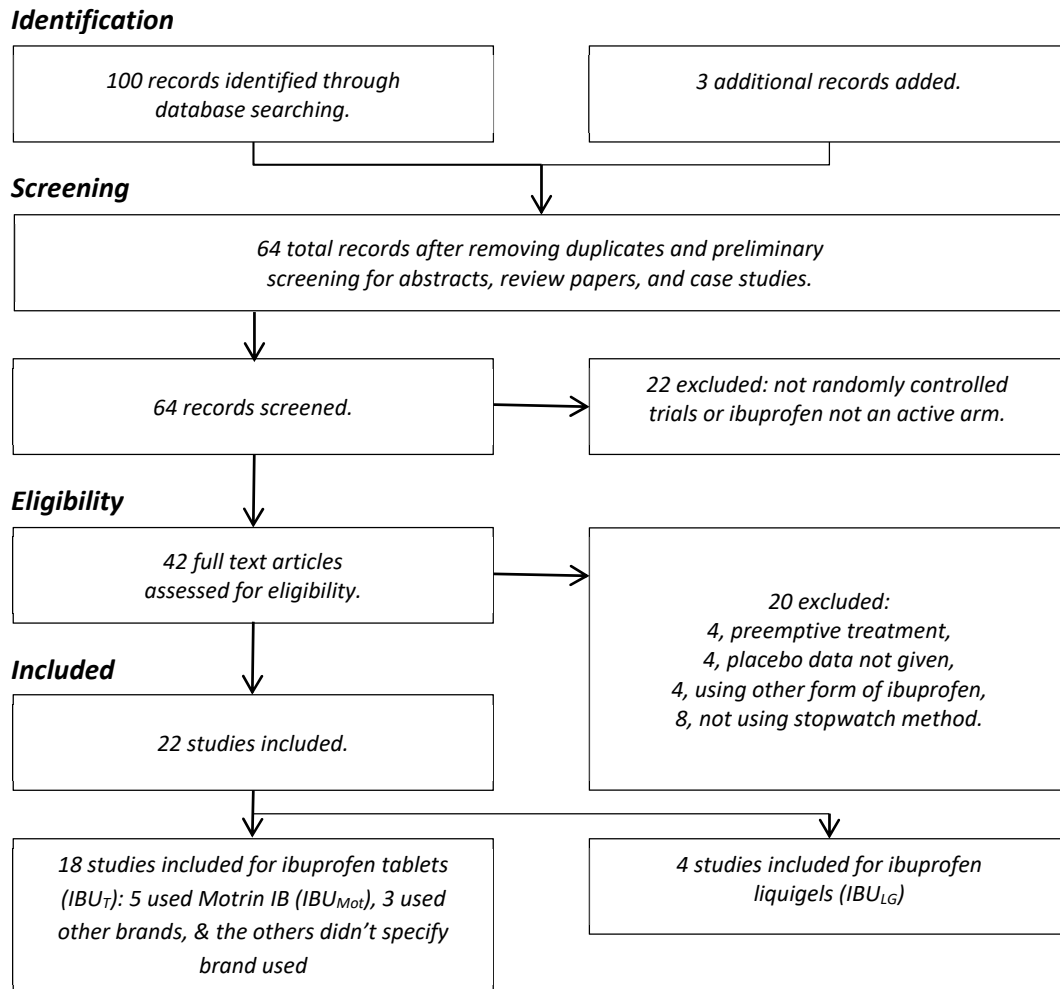


Figure 1. Flow of information in the systematic review

**Table 1.** Ibuprofen studies included in the analysis

Reference	Design	Condition	Number of patients	Reference	Design	Condition	Number of patients								
[30]	DB, P, MD	Dental	IBU <sub>LG</sub> (Advil)	74	[14]	DB, P, SD	Tension- type headache	IBU <sub>LG</sub>	60						
			Placebo	26			Placebo	32							
			Celecoxib 200 mg	74			APAP	62							
[13]	DB, P, SD	Dental	IBU <sub>LG</sub> (Advil)	67	[31]	DB, P, SD	Dental	IBU <sub>LG</sub> (Advil)	59						
			Placebo	39				Placebo	27						
			Ketoprofen 25mg	67				IBU liquigel 200 mg, APAP	61						
			APAP	66				APAP	63						
Reference	Design	Condition	Number of patients	Reference	Design	Condition	Number of patients								
[34]	DB, P, SD	Dental	IBU <sub>r</sub> (Motrin)	100	[35]	DB, P, SD	Dental	IBU <sub>r</sub> (Nurofen)	22						
			Placebo	99				Placebo	37						
			IBU <sub>r</sub> 200 mg	100				IBU Effervescent 400mg	30						
			IBU arginate 200mg	100	[36]	DB, P, SD	Dental	IBU <sub>r</sub>	46						
			IBU arginate 400mg	99				Placebo	45						
[37]	DP, P, SD	Dental	IBU <sub>r</sub> (Motrin)	87	[38]	DB, P, SD	Dental	Rofecoxib 50mg	90						
			IBU <sub>r</sub> (Advil)	86				Celecoxib 200mg	91						
			Placebo	48				IBU <sub>r</sub>	30						
			IBU Sodium	95				Placebo, IBU <sub>r</sub> 200 mg	11						
[39]	DB, P, SD	Dental	IBU <sub>r</sub>	57	[7]	DB, P, SD	Dental	IBU <sub>r</sub> (Motrin)	100						
			Placebo	57				Placebo	100						
			Celecoxib 200mg	57				IBU <sub>r</sub> 200mg	100						
IBU <sub>r</sub> 200mg	50	IBU arginate 200mg	100												
[10]	DB, P, SD	Dental	Placebo	24	[41]	DB, P, SD	Dental	Placebo	31						
			IBU <sub>r</sub> (Motrin)	52				APAP 1000 mg	34						
			IBU arginate 200mg	49				IBU <sub>r</sub> 200mg + APAP	33						
			IBU arginate 400mg	50				IBU <sub>r</sub> + APAP	67						
[40]	DB, P, SD	Tension- type headache	IBU <sub>r</sub>	99	[44]	DB, P, SD	Dental	IBU <sub>r</sub>	51						
			Placebo	48				Placebo	50						
			IBU <sub>r</sub> + Caffeine	97				Rofecoxib 50mg	50						
			Caffeine	57	[45]	DB, P, SD	Tension- type headache	IBU <sub>r</sub> (Motrin)	89						
[42]	DB, P, SD	Dental	IBU <sub>r</sub> (Advil)	50				Placebo	46						
			Placebo	25				IBU sodium 400 mg	91						
			S(+) IBU 200mg	51				[47]	DB, P, SD	Dental	IBU <sub>r</sub>	15			
			S(+) IBU 400mg	50	Placebo	16									
[43]	DB, P, SD	Migraine	IBU <sub>r</sub>	666	[49]	DB, P, SD	Dental	MK-0703 12.5mg	31						
			Placebo	220				MK-0703 50mg	28						
			ASA 250 mg + caffeine 65 mg+ APAP 250 mg	669				MK-0703 100mg	31						
			[46]	DB, P, SD				Dental	IBU <sub>r</sub>	49	[49]	DB, P, SD	Dental	IBU <sub>r</sub>	51
Placebo	50	Placebo			50										
Pregabalin 50 mg	49	Lumiracoxib 400mg			50										
Pregabalin 300 mg	50	Lumiracoxib 100mg			51										
[48]	DB, P, SD	Dental			IBU <sub>r</sub>	51	[49]		DB, P, SD	Dental				IBU <sub>r</sub>	51
					Placebo	51								Placebo	50
					Tapentadol 25mg	49								Lumiracoxib 400mg	50
					Tapentadol 50mg	50								Lumiracoxib 100mg	51
			Tapentadol 75mg	50											
			Tapentadol 100mg	48											
			Tapentadol 200mg	50											
			Morphine sulphate 60mg	51											

IBU: ibuprofen (dose is 400 mg if not specified), APAP: acetaminophen (dose is 1000 mg if not specified), ASA: aspirin  
 DB: double-blind, P: placebo-controlled, SD: single-dose, MD: multiple-dose.



**Table 3.** Median times to meaningful pain relief (MPR) for ibuprofen liquigel (IBU<sub>LG</sub>) and tablet (IBU<sub>T</sub>)

Reference	IBU <sub>LG</sub> 400 mg	Placebo	Reference	IBU <sub>T</sub> 400 mg	Placebo
	Median time, min (95% CI) <sup>a</sup>	Median time, min (95% CI) <sup>a</sup>		Median time, min (95% CI) <sup>a</sup>	Median time, min (95% CI) <sup>a</sup>
[30]	46.3 (42.4 - 61.1)	> 180	[39] <sup>c</sup>	61.0 (47.0 - 76.0)	> 180
[13]	24.2 (21.1 - 25.4)	> 180	[43] <sup>c</sup>	148 (135 - 163)	> 180
[14]	39.0 (36.8 - 41.6)	> 180	[35] <sup>c</sup>	47.4 (23.4 - 135)	> 180
[31]	28.8 (26.4 - 33.0)	> 180	[34] <sup>d</sup>	44.0	> 180
			[37] <sup>b,d</sup>	60.7, 52.0	> 180
			[10] <sup>d</sup>	48.0	> 180
<b>Pooled (weighted by sample size)</b>			[40]	161	> 180
IBU <sub>LG</sub>	35.0 (32.0 - 41.0)		[42]	35.0	> 180
<b>Pooled (inverse variance)</b>			[48]	48.0	> 180
IBU <sub>LG</sub>	31.1 (28.4 - 33.6)		[38]	52.0	> 180
			[41]	124	> 180
			[7] <sup>d</sup>	58.0	> 180
			[45] <sup>d</sup>	48.5	> 180
			<b>Pooled (weighted by sample size)</b>		
			IBU <sub>T</sub>	104	
			IBU <sub>T</sub> <sup>c</sup>	138 (125 - 156)	
			IBU <sub>MOT</sub> <sup>d</sup>	52.0	
			<b>Pooled (inverse variance)</b>		
			IBU <sub>T</sub> <sup>c</sup>	65.4 (50.1 - 90.5)	

<sup>a</sup>95% confidence interval when available; <sup>b</sup>study had two arms of ibuprofen; <sup>c</sup>studies that reported 95% CI; <sup>d</sup>Motrin IB was used in the study.

**Table 4.** Odd ratio and heterogeneity for the outcome of achieving meaningful relief at t=30, 60, 90, 120 min

Groups	Random Effect OR (95% CI)	Cochran-Q	I <sup>2</sup> (inconsistency)
<b>T=30 min</b>			
IBU <sub>T</sub> vs Placebo	1.89 (1.24 - 2.86)	n.s.	n.s.
IBU <sub>LG</sub> vs Placebo	5.90 (1.91 - 19.0)	n.s.	n.s.
IBU <sub>LG</sub> vs IBU <sub>T</sub> <sup>a</sup>	3.14 (0.91 - 10.8)		
<b>T=60 min</b>			
IBU <sub>T</sub> vs Placebo	2.76 (1.58 - 4.82)	18.5	72.9%
IBU <sub>LG</sub> vs Placebo	31.9 (14.6 - 69.7)	n.s.	n.s.
IBU <sub>LG</sub> vs IBU <sub>T</sub> <sup>a</sup>	11.6 (4.4 - 30.2)		
<b>T=90 min</b>			
IBU <sub>T</sub> vs Placebo	2.85 (1.36 - 6.00)	19.1	84.3%
IBU <sub>LG</sub> vs Placebo	55.8 (24.2 - 129)	n.s.	n.s.
IBU <sub>LG</sub> vs IBU <sub>T</sub> <sup>a</sup>	9.61 (6.39 - 60.1)		
<b>T=120 min</b>			
IBU <sub>T</sub> vs Placebo	3.67 (1.79 - 7.53)	39.1	87.2%
IBU <sub>LG</sub> vs Placebo	35.1 (16.5 - 74.7)	n.s.	n.s.
IBU <sub>LG</sub> vs IBU <sub>T</sub> <sup>a</sup>	9.56 (3.37 - 27.1)		

Pooled data are based on 3 studies for IBU<sub>LG</sub> [13, 14, 30], and on 4 studies for IBU<sub>T</sub> at t=90 min [7, 10, 34, 43], on 5 studies at t=30 min (+ [45]), and on 6 studies at t=60, 120 min (+ [40]); n.s.: values are not significant at the  $\alpha = 0.05$  level; <sup>a</sup>odd ratios of the adjusted indirect comparison.

The differences between the products was not significant at 30 min post-dose, but became significant in favour of IBU<sub>LG</sub> for all subsequent times.

Significant level of heterogeneity is observed in the outcome of time to reach MPR with the IBU<sub>T</sub> data at all times, with the exception of 30 min post dose. At 2 h post dose, for example, the Cochran-Q test significantly indicates that there is no single value for time to MPR that the different IBU<sub>T</sub> studies are evaluating, while the I<sup>2</sup> value suggests that over 87% of the total variation across studies is due to heterogeneity rather than chance. No publication bias was detected by the Egger test except for the OR of IBU<sub>T</sub> against placebo at 2 h post-dose (data not reported).

**Total pain relief and proportion of patients achieving at least 50% pain relief**

Both IBU<sub>T</sub> and IBU<sub>LG</sub> were significantly more effective in relieving pain as measured by TOTPAR (0-6 h) than placebo. The mean pooled TOTPAR score for IBU<sub>T</sub> was 13.5 (n=661, 8 studies) and 14.9 (95% CI: 14.2, 15.7, n=379, 4 studies) for data that

did not report variance and those that did, respectively. This value was 17.0 for IBU<sub>LG</sub> (95% CI: 16.0, 18.0, n=126, 2 studies) (Table 5). An independent Student’s t-test [20] reveals that IBU<sub>LG</sub> provided better pain relief as measured by TOTPAR (0-6 h) than that achieved with IBU<sub>T</sub>, although, with a small effect size (two-tailed t-test, t(503)=2.9, p=0.0042, Cohen’s d = 0.29).

The available data allowed calculation of proportion of patients with more than 50% pain relief for 2 IBU<sub>LG</sub> and 8 IBU<sub>T</sub> studies (a total of 9 included IBU<sub>T</sub> groups) (Table 6). Significantly more patients achieved at least 50% total pain relief over 6 h of dosing with either of IBU<sub>T</sub> or IBU<sub>LG</sub> than with placebo, showing an odd ratio of 11.7 (95% CI: 5.20, 26.4) with IBU<sub>T</sub> and 25.9 (95% CI: 11.4, 58.7) with IBU<sub>LG</sub> against placebo. No significant difference was observed between the two products when compared to each other. The Cochran-Q test indicates the presence of heterogeneity in the IBU<sub>T</sub> studies with regards to this outcome and the I<sup>2</sup> inconsistency tests attributes over 80% of the variation in the results to the heterogeneity or other forms of bias rather than chance.

**Table 5.** Total pain relief (TOTPAR) score over 0-6 h

Reference	IBU <sub>LG</sub> 400 mg			Placebo			Reference	IBU <sub>T</sub> 400 mg			Placebo		
	N	Mean	SD	N	Mean	SD		N	Mean	SD <sup>a</sup>	N	Mean	SD <sup>a</sup>
[13]	67	17.4	5.7	39	4.33	7.3	[39] <sup>c</sup>	57	14.9	6.2	57	3.70	5.7
[31]	59	16.6	5.8	27	5.25	7.7	[40] <sup>c</sup>	99	13.3	9.6	48	11.4	9.2
							[42] <sup>c</sup>	50	11.5	6.9	25	3.45	5.9
<b>Pooled<sup>e</sup></b>	126	17.0	5.7	66	4.71	7.4	[37] <sup>b,c,d</sup>	87	16.6	6.6	48	4.44	6.7
							[37] <sup>b,c</sup>	86	17.2	4.9			
							[34] <sup>d</sup>	100	14.9		98	6.90	
							[10] <sup>d</sup>	52	7.30		24	1.70	
							[38]	30	5.50		11	0.00	
							[7] <sup>d</sup>	100	12.4		100	4.51	
							<b>Pooled<sup>e</sup></b>	661	13.5		411	5.41	
							<b>Pooled<sup>c</sup></b>	379	14.9	7.4	178	5.94	7.8
							<b>Pooled<sup>d</sup></b>	339	13.4		270	5.11	

<sup>a</sup>Standard deviation (SD) when available; <sup>b</sup>study had two arms of ibuprofen; <sup>c</sup>studies which reported SD; <sup>d</sup>studies which used Motrin IB; <sup>e</sup>significant difference (two-tailed Student’s t-test, t(503)=2.88, p=0.0042, Cohen’s d = 0.29)

**Table 6.** Odd ratios and heterogeneity for the outcome of achieving more than 50% pain relief

Groups	Random Effect OR (95% CI)	Cochran-Q	I <sup>2</sup> (inconsistency)
IBU <sub>T</sub> vs Placebo	11.7 (5.15 - 26.4)	41.9	80.9%
IBU <sub>LG</sub> vs Placebo	25.9 (11.4 - 58.7)	n.s.	n.s.
IBU <sub>LG</sub> vs IBU <sub>T</sub> <sup>a</sup>	2.22 (0.69 - 7.06)		

Pooled data are based on two studies for IBU<sub>LG</sub> [13, 31], and on eight studies for IBU<sub>T</sub> [7, 10, 34, 37-40, 42]; n.s.: values are not significant at the α = 0.05 level; <sup>a</sup>odd ratios of the adjusted indirect comparison.

## DISCUSSION

The task of developing an analgesic medication with a meaningful onset of action has proven to be difficult if not impossible [22, 23]. This has been attributed to the gastric dysfunction that is associated with pain or the trauma of pain [22, 24]. Reports [22, 25, 26], except for one [27] suggest a reasonable correlation between analgesics concentration in the circulation and relief of pain. For an analgesic to act, however, the formulation has to disintegrate and dissolve before the active ingredient become available for absorption through the gastrointestinal (GI) tract. Although, depending on the drug pKa, the process may commence in the stomach, the main site of absorption is the intestine. In the meantime, pain and/or its trauma causes gastric dysfunction; i.e., reduced gastric motility, a slow-down of gastric emptying and reduced fluid excretion that result in slow disintegration and subsequent dissolution in the stomach [22]. Various commercially available formulations, e.g., dissolved drug in soft gelatin capsules are claimed to have rapid GI absorption, hence, quick onset of action [13]. However, clinical evidence suggestive of accelerated onset of action of products containing the same active ingredient is nonexistent or not published. Recently, a more rapid absorption during episodes of pain has been reported for formulations that are not coated and contain some disintegration action, hence, their disintegration and dissolution are less dependent on the gastric function [24]. Similarly, accelerated onset of action has been reported for products with undisclosed formulations that contain various salts of ibuprofen [28, 29]. However, such data generated by studying patients in pain are not publicly available for soft gelatin capsules. IBU<sub>LG</sub> has been compared with various other drugs for the management of pain associated with migraine, headache, or dental procedures including celecoxib [30], acetaminophen [13, 14, 31], and ketoprofen [13], but not with the other more solid formulations of ibuprofen. In the absence of comparative clinical studies, systematic reviews and indirect meta-analysis comparisons remain to be effective means of appraising clinical evidence.

Regarding a desirable onset of action, our analysis of the available data suggests, for the first time, a few advantages of liquigel over other available forms of ibuprofen. While the differences between products in FPPR were not significant (Table 2), IBU<sub>LG</sub> yielded a significantly faster MPR (Table 3). Similarly, when IBU<sub>LG</sub> was compared

with IBU<sub>T</sub> (OR=1), the OR for MPR was greater than unity (9.61 to 19.6) during 60-120 min assessment period. However, at 30 min this value was not significantly elevated for IBU<sub>LG</sub> (3.1; 95% CI: 0.90, 10.8). It is, therefore, reasonable to suggest that the liquigel exhibits a faster onset of pain relief than the other products. However, a clear difference between the products appears only at 60 min.

In healthy subjects, plasma ibuprofen concentration peaks much faster following oral administration of IBU<sub>LG</sub> ( $T_{max}$ , 30 min, [12]) than other examined products ( $T_{max}$ , 2 h, [32]). Ignoring the pathophysiological changes in response to pain [22], such a difference in the rate of absorption is expected to result in a significantly faster onset of analgesia for IBU<sub>LG</sub> as compared with IBU<sub>T</sub>. However, our analysis suggests that a significantly greater response is only seen after 60 min rather than 30 min. This delay may be attributed to the pain-induced gastric dysfunction. In addition, Jones et al [27] who correlated ibuprofen plasma concentration with its analgesic effect following administration of a soluble form of the drug found no significant link between the two variables despite their  $T_{max}$  of 30 min. Therefore, the main reasons for the delay in analgesia following oral doses appear to include i) the pain-induced gastric dysfunction, hence, delayed absorption and ii) a gap between early rise in the drug plasma concentration and its arrival at the site of action. When administered in the form of solution, ibuprofen appears to be absorbed quickly independent of gastric dysfunction as  $T_{max}$  values of 25 and 30 min have been reported for both healthy subjects [32] and patients in pain [27], respectively. This is because the drug is available for absorption without the delays caused by disintegration of tablets or opening of capsule shell and subsequent dissolution of the active ingredient. Based on our analysis, it is reasonable to suggest that during episodes of pain, although both IBU<sub>LG</sub> and IBU<sub>T</sub> are subject to delayed absorption due to the reported gastric dysfunction, the former provides a faster relief of pain relative to the latter.

In typical clinical trials of analgesics small populations of patients are employed (50-100 patients/study arm, Table 1). Considering the inherent inter-subject variability in such studies, much larger population size is needed for reliable results. By pooling the available clinical trial data that have tested the products of interest, as we have done herein, the data may be analyzed with more statistical power.



While approaches are often adopted to minimize bias in systematic reviews some sources of bias and heterogeneity that are inherent in the studies still exist [33]. In the eligible reports used in this analysis, the brand used is identified in 3 of the 4 IBU<sub>LG</sub> and only 7 out of 18 IBU<sub>T</sub> studies. This may ignore the potential between-products variability. For example, in our included reports we had 5 sets of data that identified Motrin IB (Motrin, McNeil Consumer Healthcare, Fort Washington PA, USA) as the brand. We found a shorter time to attain MPR (52.0 min) as compared to the pooled data (104.1 min) but still longer than that for IBU<sub>LG</sub> (35.0 min) (Table 3). Similarly, shorter FPPR values were observed for Motrin than that for the pooled IBU<sub>T</sub> so that it rendered the difference between Motrin and IBU<sub>LG</sub> insignificant (Table 2).

In our analysis we included all data available generated from patients with all acute type of pain (Table 1). However, the majority of the reports had included dental pain. When we analysed the available data on the dental pain only, we noticed very similar results except for FPPR that indicated a significant difference between IBU<sub>LG</sub> (10.2 min; 95% CI: 9.0, 13.8) and IBU<sub>T</sub> (26.9 min; 95% CI: 20.4, 40.3). However, this difference was based on only one study for IBU<sub>LG</sub> that reported FPPR for dental pain.

To measure efficacy, we considered total pain relief score (TOTPAR) over 6 h, which is an outcome measure that is commonly used in clinical trials of analgesia. It is based on summing a categorical pain relief scores (ranging from 0 to 4) for all participants at various time intervals after dosing. The results (Table 5) suggest that IBU<sub>LG</sub> provides a significantly higher TOTPAR as compared with IBU<sub>T</sub>, but the size of this effect is small (Cohen's  $d = 0.29$ ). Another outcome measured that is useful in determining the effectiveness of pain relieving agents is the proportion of patients with more than 50% pain relief (based on TOTPAR). This outcome can be computed according to a linear regression fit that has been developed by Moore et al [21] to dichotomize the data. The pooled odd ratio for this outcome did not indicate a significant difference between IBU<sub>LG</sub> and IBU<sub>T</sub>, which suggest that the overall efficacy across the 6 h post-dose was comparable for both products.

## CONCLUSION

The meta-analysis of the available clinical data suggests that both solid tablets and liquigel of ibuprofen are effective in controlling moderate to severe episodes of pain. The evidence, although not overwhelming, suggest a faster onset of analgesia for liquigel as compared with tablets. This information is timely in light of the ever increasing number of products in soft gelatin capsules appearing on the market. Well-powered comparative clinical trials are needed in this field.

## ACKNOWLEDGMENTS AND CONFLICTS

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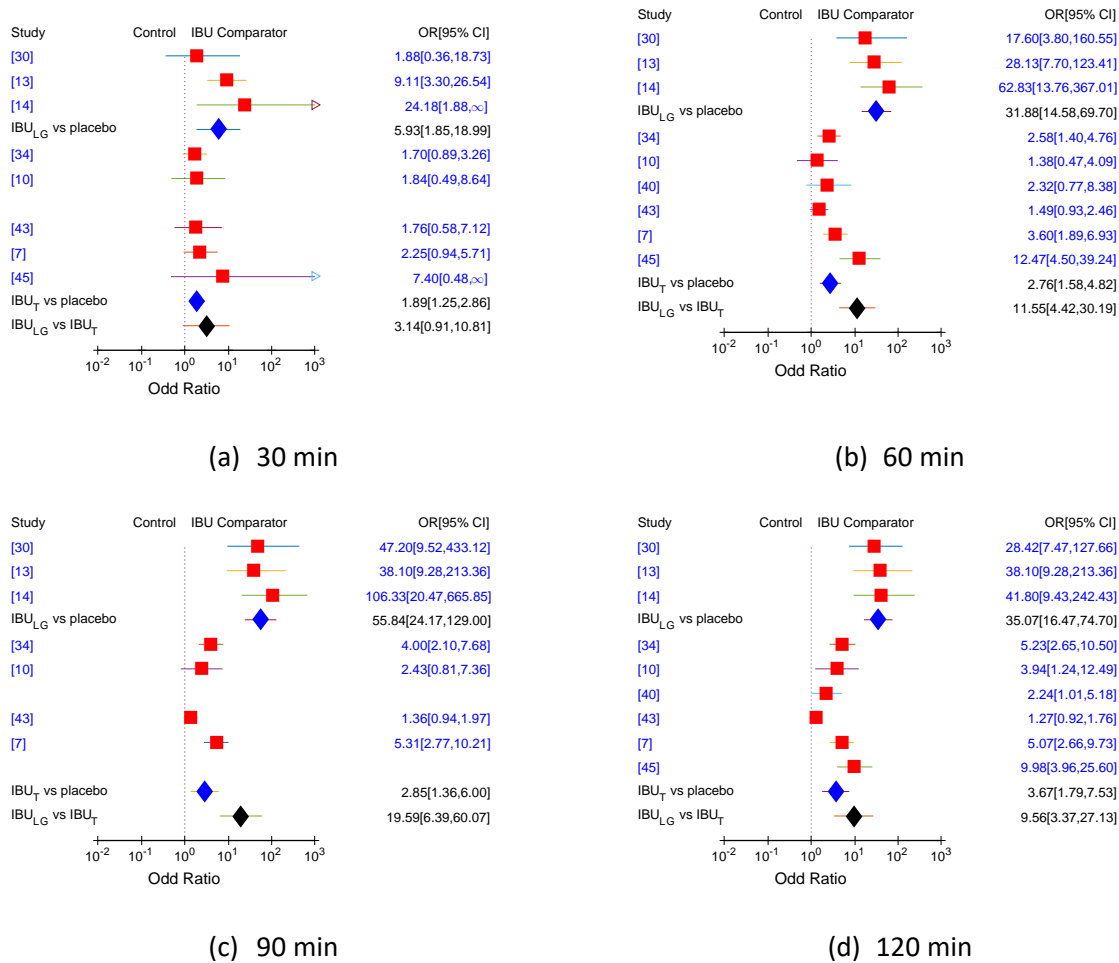
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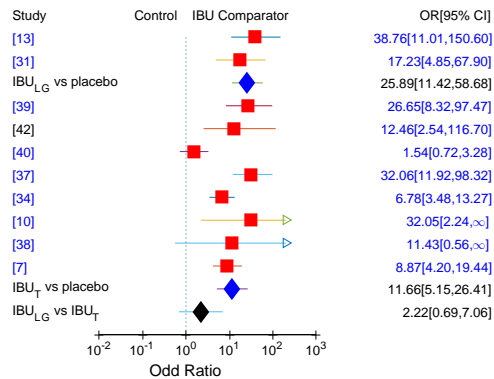
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Supplementary Material



**Figure 1S.** Forest plots of the odd ratios of achieving meaningful pain relief at (a) 30 min, (b) 60 min, (c) 90 min, and (d) 120 post dose



**Figure 2S.** Forest plot of the odd ratios of achieving at least 50% pain relief based on TOTPAR 0-6

**Table 1S.**

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	It is both (page 1)
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Done
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Last line of page 2 and beginning of page 3: "However, results ...."
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  We, therefore, attempted to compare the onset of analgesia and efficacy of the liquigel with solid dosage forms of ibuprofen by undertaking a systematic review and meta-analysis of all the studies that report onset of analgesia and efficacy of ibuprofen after administration of these formulations <a href="#">for the treatment of dental pain or migraine or tension-type headache</a> .	Page 2, paragraph just before Methods
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Protocol is with authors. The study is not registered

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3-4, Methods, paragraphs 1&2: "There was a lack .... hours post dose"
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 3, first paragraph of Methods (lines 1-3)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Pubmed search terms: Ibuprofen AND onset AND study AND (dental OR "migraine" OR "tension-type headache" OR "oral surgery")
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 3 Presented in 2 <sup>nd</sup> paragraph of Methods: "The review was .....
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  The screening and eligibility assessment of the reports was carried out independently by the two authors.	Page 3: First paragraph of Methods.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 3. The 4 <sup>th</sup> and 5 <sup>th</sup> paragraphs of Methods. "Two measures .... "
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 3. First paragraph of Methods, "The screening .... " Page 4. Bottom of page. "Variation among studies was anticipated, and due to the heterogeneity ...."

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4, 5: comparing medians to FPPR and MPR, OR of achieving meaningful relief at 30, 60, 90, 120 min post dose, differences in mean TOTPAR0-6, and OR of achieving 50% or more pain relief based on TOTPAR.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	Pages 4 & 5, “Two measures .... “

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	No evidence of bias was found. The Egger test was measured but not reported
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Subgroup analysis was used for specific brand (Motrin IB)
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5, paragraphs 1&2 and Figure 1.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not reported as no bias was found.

		Line added to the end of section 3.2. No publication bias was detected by the Egger test except for the OR of IBU <sub>T</sub> against placebo at 2 h post-dose (data not reported).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Forest plots of the odd ratios are added as supplementary figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 4,6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Egger test was used to assess publication bias and the results are described., (data are not reported)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Motrin IB data given on page 11 top 2 lines
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Main findings are summarized and incorporated within the discussion (pages 8-11)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Last paragraph on page 10: "While approaches .... "
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	This is also carried out in the discussion (pages 8-11)



<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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