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Article

Pre-emptive low-dose ketamine with local anesthesia reduces postoperative morbidity after third molar surgery: A systematic review and meta-analysis.

Ketamina en dosis bajas con anestesia local reduce la morbilidad postoperatoria de la cirugía del tercer molar: Revisión sistemática y metanálisis.

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Abstract: Objective: This review addresses a clinical research question related to lower third molar surgery (L3MS): does the combination of pre-emptive low-dose ketamine with local anesthesia (KLA) reduce postoperative complications compared with local anesthesia (LA) alone? **Material and methods:** A systematic literature search was performed to identify eligible articles by electronic searches of PubMed, Cochrane Central Register of Controlled Trials, EBSCO Library, Web of Science and grey literature through June 2019 without data or language restrictions. We analyzed all randomized controlled clinical studies (RCTs) comparing use of KLA with use of LA in L3MS regarding pain, swelling, and trismus outcomes. The quality of evidence was rated according to Cochrane's tool for assessing risk of bias. **Results:** Five RCTs encompassing 230 extraction sites (KLA = 115, LA = 115) were included in this study. The standardized mean difference (SMD) with the 95% confidence interval (CI) was used to synthesize the results. The data show that there were significant differences between the two groups in post-operative pain (SMD -1.464, 95% CI -1.683 to -0.949, p= 0.001) and swelling (SMD -0.450, 95% CI -0.758 to -0.142, p= 0.004, all low quality evidence). However, there was no significant difference in the trismus (SMD -0.754, CI -1.487 to -0.022, p = 0.043, very low quality evidence). **Conclusion:** The combination of pre-emptive low-dose ketamine with LA significantly decreased pain and swelling within the first 24 hours after L3MS compared with the control group.

Keywords: Molar, third; ketamine; trismus; pain; edema; postoperative complications

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Resumen: Objetivo: Esta revisión aborda una pregunta de investigación clínica relacionada con la cirugía del tercer molar inferior (L3MS): ¿la combinación de ketamina preventiva en dosis bajas con anestesia local (KLA) reduce las complicaciones postoperatorias en comparación con la anestesia local (AL) sola? **Material y Métodos:** Se realizó una búsqueda bibliográfica sistemática para identificar artículos elegibles mediante búsquedas electrónicas en PubMed,

Registro Cochrane Central de Ensayos Controlados, Biblioteca EBSCO, Web of Science y literatura gris hasta junio de 2019 sin restricciones de datos ni de idioma. Se analizaron todos los estudios clínicos controlados aleatorios (ECA) que compararon el uso de KLA con el uso de LA en L3MS con respecto a los resultados de dolor, hinchazón y trismo. La calidad de la evidencia se clasificó de acuerdo con la herramienta Cochrane para evaluar el riesgo de sesgo. **Resultados:** Se incluyeron en este estudio cinco ECA que abarcan 230 sitios de extracción (KLA = 115, LA = 115). La diferencia de medias estandarizada (DME) con el intervalo de confianza (IC) del 95% se utilizó para sintetizar los resultados. Los datos muestran que hubo diferencias significativas entre los dos grupos en el dolor posoperatorio (DME -1,464; IC del 95%: -1,683 a -0,949; *p*= 0,001) e hinchazón (DME -0,450; IC del 95%: -0,758 a -0,142 , *p*= 0,004, todas las pruebas de baja calidad). Sin embargo, no hubo diferencias significativas en el trismo (DME -0,754; IC: -1,487 a -0,022; *p*= 0,043, evidencia de muy baja calidad). **Conclusión:** La combinación de ketamina preventiva en dosis bajas con LA disminuyó significativamente el dolor y la hinchazón dentro de las primeras 24 horas después de la L3MS en comparación con el grupo de control.

Palabra Clave: *Tercer molar; ketamina; trismo; dolor; edema; complicaciones postoperatorias.*

INTRODUCTION.

Surgical extraction of third molar teeth is the most popular practice in oral and maxillofacial surgery, and there may be complications of this surgery, such as trismus, edema, and pain.[1,2] Different methods have been used in an attempt to prevent these problems such as chlorhexidine rinses, topical and systemic antibiotics, and low level laser therapy. In addition, preoperative medications such as corticosteroids, analgesics, muscle relaxants, and low-dose ketamine (0.1-0.5 mg/kg) have been also administreted.[3-10]

High-dose ketamine is a popular intravenous and intramuscular anesthetic agent, and low-dose ketamine finds frequent use as an intra-operative analgesic. Ketamine is a nonselective antagonist of supra-spinal N-methyl-D-aspartate (NMDA) receptors, which are involved in signaling via the excitatory neurotransmitter glutamate, and decreases neuronal signaling and has an analgesic effect.[11] However, there are variations in its effect on post-operative complications and its duration after surgery.[10,12-19]

To date, no meta-analysis has investigated the efficacy of low-dose ketamine with local anesthesia (KLA) on preventing the postoperative sequelae of lower third molar surgery (L3MS). Thus, it is possible that there is no difference between patients who received KLA and patients who received placebo and local anesthesia (LA) with respect to post-operative complications following L3MS. The purpose of this literature review was to compare the efficacy of KLA *versus* LA alone after L3MS on the post-operative complications of pain, swelling, and trismus.

MATERIALS AND METHODS.

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews was performed.[20]

This review was registered in the PROSPERO international prospective register of systematic reviews (CRD42017057604).

Focus question

The focus question of this study is the following: "Does the combination of pre-emptive low-dose ketamine and local anesthesia reduce postoperative complications after lower third molar surgery compared to local anesthesia alone?"

Search strategy

The search strategy was performed to locate all articles published up to and including June 2019 and was adapted from the PRISMA guidelines (*http://www.prisma-statement.org*).

Selection criteria

The following inclusion criteria were adopted based on the PICOS[20] criteria: the patients (P) were 18-25 years old with uni/bilateral impacted lower third molars who underwent L3MS for orthodontic, prophylactic purposes. The intervention (I) was combined with a pre-emptive low dose KLA.

The comparator (C) was placebo with LA. The major outcomes (O) were postoperative complications such as pain, facial swelling, and trismus. This study (S) evaluated RCTs and compared the effects of pre-emptive KLA with those of LA and placebo regarding postoperative L3MS complications.

Exclusion criteria

The following exclusion criteria were applied:

1) patients with systemic diseases,

2) patients with a history of allergy to ketamine,

3) studies that did not state the data required for a meta-analysis,

4) review articles, case reports, technical reports, animal or *in vitro* studies,

5) studies using sedatives with low-dose ketamine, and

6) studies comparing more than one dose of ketamine.

Data extraction

The data were extracted independently by two authors using a previously prepared data extraction form. The following data were extracted from each study: first author, year of publication, study design, patient age 21, male/female ratio, sample size, type of impacted lower third molar, outcome variables, outcomes measurement method, and follow-up time.

Quality assessment of the included research studies

A qualitative analysis of the included studies was performed independently by the two authors based on the Cochrane Handbook for Systematic Reviews of Interventions.[22] The following specific domains were used: sequence generation, allocation concealment, blinding and incomplete outcome data. The areas were recorded as 'Yes' (low risk of bias), 'Unclear' (uncertain risk of bias), or 'No' (high risk of bias). A study containing all domains was classified as having a low risk of bias.

A study missing one of these domains was classified as having a moderate risk of bias. A study missing two or more domains was considered as having a high risk of bias.

A critical appraisal of the studies was done independently by two reviewers. Any disagreements between the two review authors were resolved by consensus with a third reviewer.

Summary of measures

The predictor variables were the study and control groups. A study group consisting of patients receiving KLA and a control group composed of patients receiving placebo with LA in L3MS were examined. The outcome variables were pain via a visual analogue scale (VAS) and facial swelling and maximum mouth opening (MMO) after L3MS at different post-operative times.

Meta-analysis

The analysis was performed using standardized mean difference (SMD) values with 95% confidence intervals (CIs). Subgroup analyses were performed for all outcome variables according to different follow-up times.

The presence of significant diversity in the studies included in this analysis was formally assessed by Cochran's x^2 test and the I^2 index, where a p-value< 0.1 by the x^2 test and an I^2 value< 0.75 indicate a low degree of heterogeneity.

Alternatively, a random effects model with 95% CIs was used.[22] The null hypothesis was rejected at the 5% level (p-value< 0.05 indicating significance). The meta-analysis was calculated using comprehensive meta-analysis Biostatistics software version 2.22

Confidence of evidence

To identify the certainty of effect estimates from the meta-analysis for the outcomes of interest the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach of meta-analysis[23] was used. In the GRADE system, RCTs begin as high-quality evidence, but may be down-rated due to limitations in the study design (risk of bias). The limitations could be inconsistency, imprecision, indirectness, and publication bias.[24] Summary of confidence for the present evidence was estimated using the GRADEpro Guideline Development Tool (GDT) online software. Avalaible at: https://gdt.gradepro.org/app/.[25]

RESULTS.

Results of literature search

Figure 1 shows the process of screening articles for inclusion in the meta-analysis. The search strategy yielded 155 articles from all databases, and 29 additional articles were identified through a manual search. Thirty-three of the 184 total articles were excluded due to duplication, and 137 articles were excluded after reading the titles and abstracts.

The remaining 14 full-text articles were reviewed independently for eligibility. An additional 9 studies were excluded because they did not meet the inclusion criteria. Therefore, 5 RCTs were included in the final analysis.[10,16-19]

Description of included studies

The detailed data of all the RCTs included in this review are listed in Table 2. There were three parallel clinical studies[10,16,17] and two split mouth studies18, 19 included in the meta-analysis. There were 230 extraction sites enrolled in the five studies, and there were 115 extraction sites in the KLA group and 115 extraction sites in the control group.

There were four studies that used Pederson's difficulty

index to determine the difficulty of treating the affected lower third molars.[16-19]

There were four studies that measured pain by a VAS of 0-1010,[16,17,19] and one study measured it by a VAS of 0-100. The follow-up period varied between 30 minutes and seven days. There were four studies that measured facial swelling in millimeters using the Gabaka & Matsumara method.[10,16,17,19] One study measured facial swelling in millimeters with the Schultze-Mosgau method. The follow-up period for this outcome varied between one and seven days.

All studies measured MMO using the maximum incisal opening in millimeters,[10,16,19] and the follow-up period for MMO varied between one and seven days.

Risk of bias within included studies

Four studies were judged to have a low risk of bias (high quality),[10,17-19] and one study was considered to have a moderate risk of bias.[16] Additional details regarding study bias are shown in Table 2.

Certainty of evidence

The quality of evidence of this sematic review and meta-analysis estimates for all analyses varied from low to very low.

The evidence was downgraded because of study limitations, imprecision. More details about the quality of evidence for all outcomes based on the GRADE system are summarized in Table 3.

RESULTS OF OUTCOME VARIABLES

1. Pain via VAS

A total of 230 extraction sites were enrolled in five studies that assessed the difference in pain between the KLA group and controls following L3MS.[10,16-19] The follow-up period varied between 30 minutes and seven days.

1.1 Pain 30 min post-operatively

Three studies assessed pain 30 minutes after L3MS, and there were 75 KLA subjects (extraction sites) and 75 controls included in these studies.[10,17,18]

The subjects receiving KLA had significantly less pain than controls (SMD -1.164, 95% CI -2.055 to -0.273, p=0.010).

A random effects model was used due to the study heterogeneity.

1.2 One hour post-operatively

Three studies assessed the difference in pain one hour following L3MS and assessed 75 KLA subjects and 75 controls.[10,17,18] The subjects receiving KLA had significantly less pain than controls (SMD -1.776, 95% CI -2.736 to -0.518, p=0.001).

There was heterogeneity among the studies, and a random effects model was used.

1.3 Twelve hours post-operatively

Three studies assessed the difference in pain 12 hours following L3MS, and there were 75 KLA subjects and 75 controls in these studies.[10,17,18] The subjects receiving KLA did not report significantly less pain than controls (SMD -1.941, 95% CI -3.86 to -0.81, p=0.048).

There was heterogeneity among studies, and a random effects model was used.

1.4 Postoperative day one

Four studies assessed the difference in pain on postoperative day one with a total of 100 KLA subjects and 100 controls in these studies.[10,17,19] The subjects receiving KLA did not report significantly less pain than controls (SMD -4.446, 95% CI -1.56 to -0.156, p= 0.152). There was heterogeneity among studies, and a random effects model was used.

1.5 Postoperative day two

Two studies assessed the difference in pain on postoperative day two, and there were 40 KLA subjects and 40 controls in these studies.[16,19] The subjects receiving KLA had significantly less pain than controls (SMD -1.166, 95% CI -3.275 to -0.047, p= 0.044).

There was heterogeneity among studies, and a random effects model was used.

The overall cumulative analysis shown in Figure 2 indicates that the five studies showed a significant difference between the two groups for all follow-up times after L3MS (SMD -1.464, 95% CI -1.983 to -0.946, p=0.0001, low quality evidence).[10,16-19]

2. Facial swelling in millimeters

A total of 230 extraction sites in the five studies were assessed for differences in facial swelling between the KLA group and controls following L3MS.[10,16-19]

The follow-up period for this outcome varied between one and seven days.

2.1 Postoperative day one

Four studies assessed the difference in facial swelling on postoperative day one and included 100 KLA subjects and 100 controls.[10,17-19]

The subjects receiving KLA had significantly less facial swelling than controls (SMD -0.632, 95% CI -1.204 to -0.060, p=0.030). There was heterogeneity among studies, and a random effects model was used (Figure 3).

Figure 1. Flow chart of study selection process based on PRISMA guidelines.

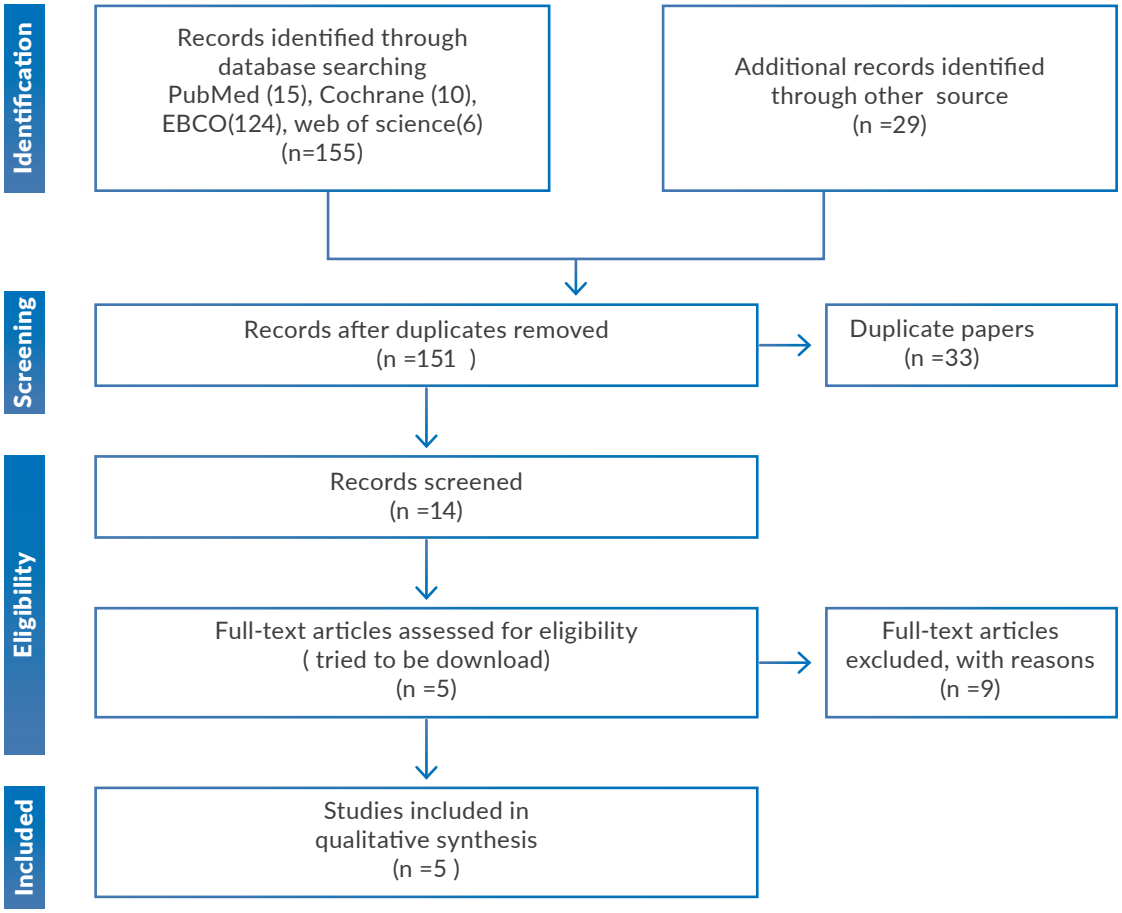

Figure 2. KLA *versus* LA alone after L3MS, pain.

Study name	Year	Subgroup within study	Statistics for each study: Std diff in means	Lower limit	Upper limit	*p*-value
Satilmiş *et al.*,[10]	2009	1 day	-0.831	-1.409	-0.253	0.005
Kumar *et al.*,[17]	2015	1 day	0.141	-0.366	0.648	0.585
Hadhimane *et al.*,[18]	2016	1 day	-3.406	-4.376	-2.438	0.000
Shah *et al.*,[19]	2016	1 day	-1.098	-1.692	-0.503	0.000
Total			**-1.239**	**-2.413**	**-0.064**	**0.039**
Satilmiş *et al.*,[10]	2009	1 hour	-2.500	-3.240	-1.761	0.000
Hadhimane *et al.*,[18]	2016	1 hour	-1.982	-2.716	-1.208	0.000
Kumar *et al.*,[17]	2015	1 hour	-0.950	-1.484	-0.416	0.000
Total			**-1.776**	**-0.736**	**-0.815**	**0.000**
Kumar *et al.*,[17]	2015	12 hour	-0.192	-0.699	0.315	0.458
Satilmiş *et al.*,[10]	2009	12 hour	-2.215	-2.920	-1.511	0.000
Hadhimane *et al.*,[18]	2016	12 hour	-3.520	-4.509	-2.530	0.000
Total			**-1.941**	**-3.863**	**-0.018**	**0.048**
Hesham *et al.*,[14]	2014	2 day	-2.532	-3.493	-1.572	0.000
Shah *et al.*,[19]	2016	2 day	-0.882	-1.463	-0.302	0.003
Total			**-1.661**	**-3.275**	**-0.047**	**0.044**
Satilmiş *et al.*,[10]	2009	30 min	-1.700	-2.347	-1.053	0.000
Kumar *et al.*,[17]	2015	30 min	-0.357	-0.867	0.154	0.171
Hadhimane *et al.*,[18]	2016	30 min	-1.502	-2.204	-0.800	0.000
Sub-Total			-1.164	-2.055	-0.273	0.000
Total			**-1.464**	**-1.983**	**-0.946**	**0.000**

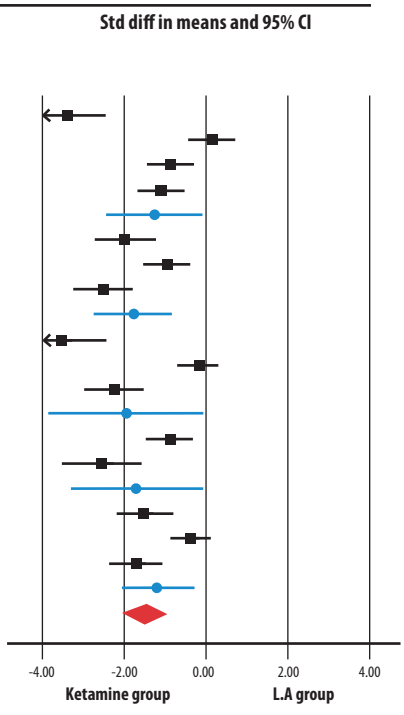

Figure 3. KLA *versus* LA alone after L3MS, facial swelling.

Study name	Year	Subgroup within study	Statistics for each study: Std diff in means	Lower limit	Upper limit	*p*-value
Satilmiş *et al.*,[10]	2009	1 day	-1.473	-2.098	-0.061	0.000
Kumar *et al.*,[17]	2015	1 day	-0.097	0.603	0.409	0.707
Hadhimane *et al.*,[18]	2016	1 day	-0.388	-1014	0.237	0.224
Shah *et al.*,[19]	2016	1 day	-0.629	-1.196	-0.061	0.030
Total			**-0.632**	**-1.204**	**-0.060**	**0.030**
Hesham *et al.*,[14]	2014	2 day	-0.171	-0.888	0.546	0.640
Shah *et al.*,[19]	2016	2 day	-0.335	-0.893	0.223	0.239
Total			**-0.273**	**-0.714**	**0167**	**0.224**
Satilmiş *et al.*,[10]	2009	3 day	-2.942	-3.742	-2.142	0.000
Kumar *et al.*,[17]	2015	3 day	-0.036	-0.542	0.470	0.890
Hadhimane *et al.*,[18]	2016	3 day	0.025	-0.595	0.645	0.937
Total			**-0.960**	**-2.621**	**0.702**	**0.258**
Satilmiş *et al.*,[10]	2009	7day	-1.738	-2.388	-1.087	0.000
Kumar *et al.*,[17]	2015	7 day	-0.157	-0.664	0.349	0.543
Hadhimane *et al.*,[18]	2016	7 day	-0.111	-0.731	0.509	0.725
Shah *et al.*,[19]	2016	7 day	-0.201	-0.757	0.355	0.478
Sub-Total		7 day	-0.537	-1.252	0.178	0.141
Overall			**-0.450**	**-0.758**	**-0.142**	**0.004**

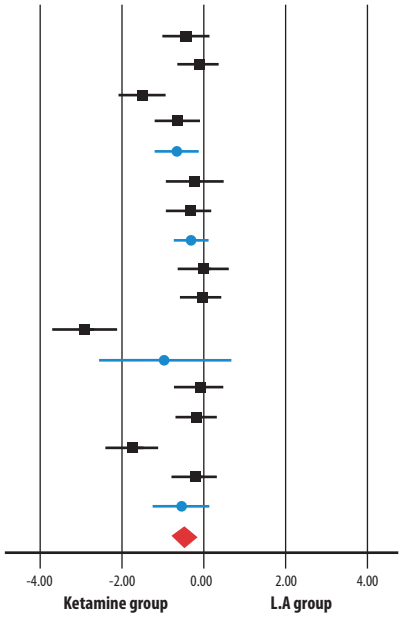

Figure 4. KLA *versus* LA alone after L3MS, MMO.

Study name	Year	Statistics for each study: Std diff in means	Lower limit	Upper limit	*p*-value
Hadhimane *et al.*,[18]	2016	-0.185	-0.806	0.436	0.560
Kumar *et al.*,[17]	2015	0.969	0.434	1.504	0.000
Satilmiş *et al.*,[10]	2009	-3.053	-3.869	-2.237	0.000
Shah *et al.*,[19]	2016	0.027	-0.528	0.581	0.925
Total		**-0.534**	**-1.979**	**0.911**	**0.469**
Hesham *et al.*,[14]	2014	-1.584	-2.382	-0.747	0.000
Satilmiş *et al.*,[10]	2009	-0.040	-0.594	0.514	0.888
Total		**-0.771**	**-2.264**	**0.721**	**0.311**
Hadhimane *et al.*,[18]	2016	-0.884	-1.533	-0.235	0.008
Kumar *et al.*,[17]	2015	0.532	0.017	1.047	0.043
Satilmiş *et al.*,[10]	2009	-4.780	-5.869	-3.692	0.000
Total		**-1.664**	**-4.174**	**0.846**	**0.194**
Hadhimane *et al.*,[18]	2016	0.000	-0.620	0.620	1.000
Kumar *et al.*,[17]	2015	0.666	0.147	1.186	0.012
Satilmiş *et al.*,[10]	2009	-3.072	-3.891	-2.254	0.000
Shah *et al.*,[19]	2016	-0.089	-0.644	0.465	0.752
Sub-Total		-0.695	-1.828	0.438	0.229
Overall		**-0.754**	**-1.487**	**-0.022**	**0.043**

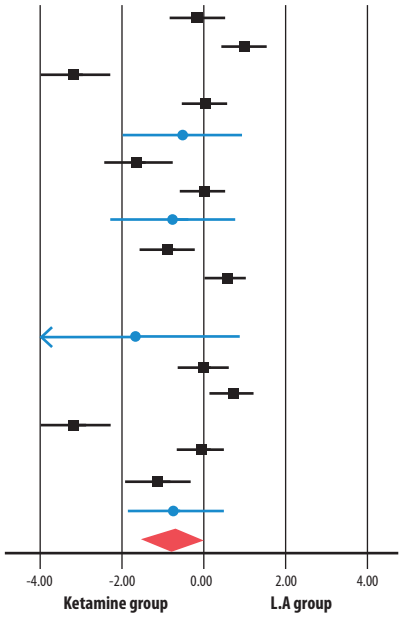

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Table 1. Characteristics of the included studies.

Authors Years	Study design	Male to female	Patients age ratio (average)	Number and sex patients M	F	Type of impacted third molars	Flaps of designs	Dose of ketamine	Type of local anesthesia	Outcome used	Type of variables assessment	Follow up
Satilmiş et al.,[10] 2009	-RCT Parallel blinded	24 : 26	-17 -39 Year	24	26	N.M	N.M	Low dose 0.3mg/kg	4% Articaine HCL +epinephrine 1/100.000	Pain Facial swelling (mm) Trismus (mm)	VAS (0-10) Gabaka & Matsumara Distance between incisal edges of upper and lower incisor	At 30 Min, 1, 4, 12 hrs, and 1d At 1,3, and 7 ds At 1,3, and 7 ds
Hesham et al.,[14] 2014	-RCT Parallel -Double blinded	11 : 4	18 - 30 Year	22	8	Moderately and difficult impaction asper Pederson's difficulty index	Full thickness mucoperiosteal flap	Low dose 0.3mg/kg + epinephrine	4% articaine HCL (mm) 1/100.000	Pain Facial swelling & Matsumara Trismus (mm)	VAS (0-10) Gabaka At 2,5, and 7 ds Distance between incisal edges of upper and lower incisor	At 2,5, and 7 ds At 2,5, and 7 ds
Kumar et al.,[17] 2015	-RCT -Parallel -Double blinded	N. M	18 - 38 Year	N. M		Moderately difficult impaction as per Pederson's difficulty index	A standard Terrance Ward incision was placed and a full thickness mucoperiosteal flap was reflected	Low dose 0.3mg/kg	2% lignocaine + adrenaline 1/80.000	Pain Facial swelling (mm) Trismus (mm)	VAS (0-10) Gabaka & Matsumara Distance between incisal edges of upper and lower incisor	At 30min, 1, 4, 12 hrs, and 1d At 1,3,and 7 ds At 1,3,and 7 ds
Hadhimane et al.,[18] 7, 2016	-RCT -Split mouth -Double blinded	13 : 7	18 - 31 Year	13	7	Moderately difficult impac-tion as per pederson's difficulty index	Full thickness mucoperiosteal flap	Low dose 0.5mg/kg	2% lignocaine + adrenaline 1/80.000	Pain Facial swelling (mm) Trismus (mm)	VAS (0-100) Schultze-Mosgau Distance between incisal edges of upper and lower incisor	At 30min, 1, 4, 12hrs, 1, 3, and 7ds At 1,3, and 7 ds At 1,3, and 7 ds
Shah et al.,[19] 2016	-RCT -split mouth -double blinded	13 : 12	18 - 50 Year	13	12	By per Pederson's difficulty index	A standard Terrance Ward incision was placed and a full thickness mucoperiosteal flap was reflected	Low dose 0.2mg/kg	2% lignocaine + epinephrine 1/100.000	Pain Facial swelling (mm) Trismus (mm)	VAS (0-10) Gabaka & Matsumara Distance between incisal edges of upper and lower incisor	At 1,2,and 7 ds At 1,2,and 7 ds At 1,2,and 7 ds

Table 2. Critical appraisal of included studies.

Author	Year	Random sequence generation	Allocation concealment	Masking	Discussion of incomplete outcome data	Selective reporting bias	Other apparent	Score	Quality
Satilmiş *et al.,*[10]	2009	Unclear	Low	Low	Low	Low	Low	11	High
Hesham *et al.,*[14]	2014	High	High	Low	Low	High	Low	6	Medium
Kumar *et al.,*[17]	2015	Unclear	Unclear	Low	Low	Unclear	Low	9	High
Hadhimane *et al.,*[18]	2016	Unclear	Unclear	Low	Low	Low	Low	10	High
Shah *et al.,*[19]	2016	Unclear	Unclear	Low	Low	Low	Low	10	High

Low indicates a score of 2. Unclear, a score of 1; and high, a score of 0. † Quality was categorized as low (score 1-4), medium (score 5-8), or high (score 9-12).

Table 3. Low indicates a score of 2; unclear, a score of 1; and high, a score of 0.
† Quality was categorized as low (score 1-4), medium (score 5-8), or high (score 9-12).

		Certainty assessment					No. of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[KLA]	[control]	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Posttreatment pain intensity- KLA versus control (follow up: 30 min postoperatively to 2 days postoperatively ; assessed with: VAS)												
5	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	230	**230**	------	trials-1.4 SD lower (-2 lower to -1.9 lower) LOW	⨁⨁◯◯ LOW	------
Facial swelling- KLA versus control , one day postoperatively to 7 days postoperatively												
5	randomised trials	very serious[a,b]	not serious	not serious	serious[c]	none	230	**230**	------	SMD -0.75 SD higher (-1.4 higher to -0.022 higher)	⨁⨁◯◯ LOW	------
Maximal mouth opening - KLA versus control , one day postoperatively to 7 days postoperatively												
5	randomised trials	serious[d]	not serious	not serious	serious[c]	none	230	**230**	------	SMD -0.75 SD higher (-1.4 higher to -0.022 higher)	⨁◯◯◯ Very low	------

CI: Confidence interval. **SMD:** Standardized mean difference. [a]: Drop out. [b]: Small sample size. [c]: Cross null. [d]: Risk of bias. [e]: Long CI.

2.2 Post-operative day two

There were two studies that assessed the difference in facial swelling on postoperative day two, and these studies included 40 KLA subjects and 40 controls.[16,19]

The subjects receiving KLA had significantly less facial swelling than controls (SMD -0.273, 95% CI -0.714 to -0.167, p=0.001). There was heterogeneity among studies, and a random effects model was used (Figure 3).

2.3 Postoperative day three

Three studies assessed the difference in facial swelling on postoperative day three and included 75 KLA subjects and 75 controls.[10,17,18]

The subjects receiving KLA did not report significantly less facial swelling than the controls (SMD -0.955, 95% CI -2.565 to 0.655, p=0.245). There was heterogeneity among studies, and a random effects model was used (Figure 3).

2.4 Postoperative day seven

All five studies assessed the difference in facial swelling on postoperative day seven, and there were a total of 115 KLA subjects and 115 controls.[10,16-19] There was no significant difference between the two groups on the seventh day following L3MS (SMD -0.537, 95% CI -1.252 to 0.178, *p*=0.141). There was heterogeneity among studies, and a random effects model was used (Figure 3).

The overall cumulative analysis shown in Figure 3 indicates that the five studies show a significant difference between groups at all follow-up times after L3MS.10, 16-19 (SMD -0.450, 95% CI -0.758 to -0.142, *p*=0.004, low quality evidence).

3. Maximal mouth opening in millimeters

A total of 230 extraction sites were enrolled in five studies that evaluated the difference in MMO between the KLA group and the controls following L3MS.[10,1619] The follow-up period varied between one and seven days.

3.1 Postoperative day one

Four studies assessed the difference in MMO on postoperative day one, and there were 100 KLA subjects and 100 controls in these studies.[10,17-19] There was no significant difference between the two groups one day following L3MS (SMD -0.534, 95% CI -1.979 to -0.911, *p*=0.469). There was heterogeneity among studies, and a random effects model was used (Figure 4).

3.2 Postoperative day two

There were two studies evaluating the difference in MMO on postoperative day two, and there were 40 cases in the KLA group and 40 controls in these studies.[16,19] There was no significant difference between the groups two days after L3MS (SMD -0.771, 95% CI -2.264 to -0.721, *p*=0.331). There was heterogeneity among studies, and a random effects model was used (Figure 4).

3.3 Postoperative day three

Three studies assessed the difference in MMO on postoperative day three, and there were 75 patients in the KLA group and 75 controls.[10,17,18] There was no significant difference between the two groups (SMD -1.664, 95% CI -4.17 to -0.845, *p*=0.194). There was heterogeneity among studies, and a random effects model was used (Figure 4).

3.4 Postoperative day seven

All five studies assessed the difference in MMO on post-operative day seven and included a total of 115 KLA subjects and 115 controls.[10,16-19] There was no significant difference between the two groups (SMD -0.694, 95% CI -1.828 to -0.438, *p*=0.229). There was heterogeneity among studies, and a random effects model was used (Figure 4).

The cumulative analysis for all five studies shown in Figure 4 indicates there was no significant difference between the two groups at the different follow-up times (SMD -0.754 95% CI -1.487 to -0.022, *p*=0.043, very low quality evidence).[10,16-19]

DISCUSSION.

The objective of this study was to use meta-analysis to systematically compare patients who received KLA with those who received LA alone after L3MS and then to evaluate postoperative complications. This is the first systematic review and meta-analysis comparing the analgesic and anti-inflammatory efficacies of KLA versus LA alone following L3MS.

The main finding of this study was the significant reduction in pain at 24 hours after L3MS in the KLA group compared to that in the LA group. The overall cumulative analysis showed substantial pain reduction in KLA cases compared to that in LA cases (SMD -1.464, 95% CI -1.464 to -0.949, *p*=0.001, low quality evidence).

There was also a significant reduction in the postoperative facial swelling at the first postoperative day. However, there was no significant difference in facial swelling after the third or seventh postoperative days. The overall cumulative analysis revealed that there was a significant difference in favor of the study group (SMD -0.450, 95% CI -0.758 to -0.142, p = 0.004, low quality evidence).

Finally, there was no significant difference in MMO between the two groups after any of the follow-up times(very low quality evidence).

The results of the current study were consistent with previous studies.[10,16-19,26-29] However, several reports show contrasting results.[13,29-32] These differences might be due to an additive analgesic effect of ketamine.[33,34] This study confirmed that the analgesic effect of low-dose ketamine following L3MS lasted for the first 24 hours, as reported by previous studies.[30,35-37]

There are several limitations of this study, including the following:

1) confounding factors were not controlled for within the included studies, such as the experience of surgeons, the length of surgical time, type of impaction,

the amount of bone removed, type of incision and patient age; and

2) different doses of pre-emptive ketamine were used in the included studies. Three studies used 0.3 mg/body weight,[10,16,17] and the two remaining studies used 0.519 and 0.218 mg/body weight.

The strengths of this study were the following:

1) this is the first systematic review and meta-analysis of RCTs assessing the efficacy of the pre-emptive use of low-dose ketamine after L3MS compared to a control group;

2) the type of evidence provided by this study was type I;

3) four studies had a low risk of bias, and one study had a moderate of bias based on the result of a critical appraisal of the RCTs; and

4) the subgroup analyses were performed according to the different follow-up times to identify the exact analgesic and anti-inflammatory effects of ketamine;

5) to avoid over/underestimation of evidence, GRADE system to assess certainty of the yield evidence was performed.

There are different routes of administration for ketamine, which include intravenous, intramuscular, subcutaneous and submucosal. Thus, it is important to determine whether there are any differences in analgesic or anti-inflammatory effects of ketamine due to the different routes of administration.

The data indicate there was no significant difference in pain scores when sub-anesthetic low-dose ketamine was provided through systemic, local or intravenous delivery.[37-40] In the current study, a low dose of ketamine was administered locally in combination with a local anesthetic agent. An analgesic effect of ketamine after submucosal injection can be explained by the fact that the drug is an antagonist of NMDA receptors and has a known peripheral mechanism.[41]

The substantial reduction in pain and facial swelling observed 24 hours after L3MS can be attributed to the state of dissociative anesthesia via NMDA receptor inhibition and the anti-inflammatory properties associated with antagonizing the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin.[6,42-46]

In conclusion, the results of this meta-analysis provide low quality evidence to support that KLA produces a significant reduction in pain and swelling with no substantial changes in trismus within the first 24 hours after L3MS compared with a control group (very low quality evidence). Further multicenter RCTs with larger sample sizes based on sample size calculations that control for all possible confounding factors at baseline should be performed.

These studies should consider both cost and postoperative complications. Additionally, different routes (submucosal, combined with local anesthesia, intravenous or intramuscular) and doses of ketamine should be compared to placebo, corticosteroids, or other analgesics after L3MS.[27]

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