

Effectiveness Of Immediate Complete Anterior Guidance Development In Reducing Disclusion Time In Patients With Chronic Myofascial Pain Dysfunction: A Systematic Review And Meta-Analysis

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Abstract

Statement of problem. Multiple etiological factors contribute to chronic myofascial pain dysfunction, yet most associated factor is occlusal instability or non-equilibrium causing facial muscular pain. Although various treatment modalities have been in practice, one of the promising methods, to treat such patients is immediate complete anterior guidance development (ICAGD) which focuses on disclusion time reduction (DTR) of posterior teeth, relieving the patients of painful symptoms.

Purpose. The purpose of this systematic review and meta-analysis is to determine if ICAGD is effective in reducing disclusion time to reduce symptoms in patients with chronic myofascial pain dysfunction.

Material and methods. Electronic search of PubMed (including MEDLINE), Cochrane Central database, Scopus, Lilacs, and Google Scholar search engine for articles published from 1st January 1980 to 1st January 2023 was conducted. Studies were chosen based on the inclusion criteria, which included the participants treated using ICAGD for chronic myofascial pain dysfunction, reduced disclusion time in patients who were treated with ICAGD and other methods, changes in pain score, difficulty in chewing, morning jaw stiffness, etc. The methodological qualities of included studies were investigated by Cochrane ROB 2 for randomized control trials, ROBINS-I for non-randomized trials, JBI checklist for case reports and new castle-Ottawa for observational cohort studies. Metadisc 1.4 and RevMan 5.3 were used to conduct the meta-analysis.

Results. Twenty-six studies were included in this systematic review and a meta-analysis of five articles was done after applying the inclusion and exclusion criteria. Most of the included studies showed low risk of bias. In randomized controlled trials, the main source of bias was in performance and assessment bias and in non-randomized controlled trials, the main source of bias was in selection of study participants.

Conclusion. This systematic review and meta-analysis suggest ICAGD can be employed in patients with temporomandibular disorders. The symptoms including muscular pain, jaw stiffness, functional restrictions were all improved within a week of application of ICAGD and sustained for more than 6 months. Primarily, it reduces disclusion time which is responsible for the painful symptomatology associated with chronic myofascial pain dysfunction. It is an easy to perform therapy with high degree of patient acceptance as compared to other treatment modalities available to treat such patients. Therefore, suggesting the application of ICAGD for treatment of chronic myofascial pain dysfunction. Although, evidence acquired till date needs to be standardized as well further research is required to provide stronger evidence.

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I. Clinical Implication

The presentation of significant evidence to support ICAGD as an effective treatment modality for chronic myofascial pain dysfunction, should encourage the practitioners and researchers to delve deeper into using this as the primary treatment option for such patients to make it a routine procedure.

II. Introduction

Pain is the most common symptom for which patients visits the dental clinic and along with dental pain there is also a component of musculoskeletal pain which arises surrounding orofacial musculature and temporomandibular joint. Myofascial pain is one of the most common causes of chronic Orofacial pain (Edmiston and Larsen, 1978). Myofascial pain syndrome (MPS) refers to a type of chronic pain that occurs in muscles, fascia or related soft tissues and can be accompanied by obvious emotional disorders or dysfunctions.^[1] It is commonly associated with persistent regional pain such as backache, shoulder pain, headaches, facial pain, and earache, etc.^[2]

It is extremely difficult to pinpoint the etiological factors for MPS due to its multifactorial nature. The current hypothesis for occurrence of MPS attributes the pain to the stimulation of sensory nerves in the inflammatory environment and compression of oedematous tissues due to inflammation.^[1] Most frequently described aetiologies include postural stresses, inefficient biomechanics, and repetitive overuse. Along with these, occlusal instability has long been considered as an important aetiological factor. Interferences in occlusion can produce tooth pain, masticatory muscle hyperactivity and tooth mobility in extreme cases. Equilibration of occlusion has been advocated as a successful treatment modality by several authors.^[3]

To choose a best course of therapy to treat such patients a detailed history and clinical examination plays an important role. Various treatment modalities have been documented in the literature ranging from non-invasive procedures including pharmacological therapy, ultrasonic therapy, laser application to invasive procedures such as dry needling, TENS therapy, steroid injections etc.^[4] There is also a recommendation for psychological intervention with Cognitive Behavioural Therapy, in order to reduce a patient's stress which in turn will reduce clenching and grinding habits, while improving their emotional behaviour. But there is no strong evidence present to support the use of this method.^[5]

One source of painful muscular symptomatology in MPS is elevated excursive masseter and temporalis muscle activity. Electromyographic studies tried to explain the association between hyperactivity of masticatory muscles which leads to longer disclusion time.^[6] Disclusion time is defined as the duration for which working-side and nonworking-side molars and nonworking-side premolars are in contact during an excursive movement.^[7] Longer the disclusion time more will be the compressions of the periodontal ligament mechanoreceptors leading to pain. It was first measured with T-scan instrument. A study involving T-scan and occlusal adjustment revealed that when this disclusion time was reduced to <0.4 seconds the contraction levels of muscles were significantly reduced.^[6,8]

To shorten this disclusion time, occlusal adjustment procedure has been employed. Traditionally performed occlusal equilibration is a subjective procedure, depend on the operator assessment, and an unmeasured technique focusing on locating centric relation to relieve occlusal interferences using articulating papers. An alternate procedure which is more accurate and measurement driven, named ICAGD whose primary goal is to decrease the time required for all posterior teeth during mandibular excursion has been shown to be successful in many patients.^[9] T-Scan occlusal analysis system helps to measure this time. It helps in measuring the 1st contact of maximum intercuspsation during bilateral closure, which ensures that no tooth contacts early, absorbing excessive loads.^[10]

ICAGD technique is more précis as compared to traditional occlusal equilibration as it minimizes subjective occlusal end-results. This technique was first described by Kerstein and Farrell. Multiple studies with ICAGD treatment show that once the hyperactivity is decreased, rapid dysfunctional muscular TMD symptom resolution occurs.^[11] Application of ICAGD to reduce disclusion time has also been studied for bruxism, mastication smoothness, postural instability, depression studies, etc.^[5,12,13]

Hence the purpose of this systematic review and meta-analysis was to assess the effectiveness of ICAGD in reducing disclusion time to reduce symptoms in patients with chronic myofascial pain dysfunction. The null hypothesis formulated for the study was there is no effect of ICAGD on disclusion time reduction in patients with chronic myofascial pain dysfunction.

III. Material And Methods

This systematic review has been carried out with respect to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines. The protocol for the systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO-CRD42022357399) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist.^[14]

The following research question addressed by using PICOS which is Population, Intervention, Comparison, Outcome, and Study design^[15] (Table 1) was “Is Immediate Complete Anterior Guidance Development effective in reducing disclusion time in patients with chronic myofascial pain dysfunction?”.

The concept table was made based on PICO criteria which includes the key concepts, Mesh terms as well as free text terms. Electronic search of PubMed (including MEDLINE), Cochrane Central database, Google Scholar Lilacs, Scopus, and Science Direct search engine for articles published from 1st January 1980 to 1st January 2023 was conducted independently by three authors namely (S.K.K. and A.M.G. and A.K.G.) by using the key concept table and MeSH (Medical Subject Headings) terms (Table 2). Moreover, the manual search was performed in high-ranking journals in the field of temporomandibular disorders like the journal of craniomandibular practice, Advance dental technologies and techniques and Sensors. Reference list of included articles were thoroughly scrutinized by two review authors.

According to previously established protocol, the search and screening were conducted by 3 review authors (S.K.K., A.M.G. and A.K.G.). In phase one, the titles and abstracts of all the articles were reviewed. Phase two consisted of selection of full text articles which were independently reviewed and screened by the same reviewers. Any disagreement was resolved by discussion. Fourth reviewer (J.N.) was involved to make final decision, when mutual agreement between 3 reviewers was not reached. Final decision was based on consensus amongst all 4 authors. Studies on patients with chronic myofascial pain dysfunction who were treated with ICAGD and other treatment modalities were included in the study. Randomized clinical control trials, non-randomized controlled trials, case control studies, case reports on chronic myofascial pain dysfunction ICAGD and disclusion time reduction were included in the study. Clinical trials or in-vivo studies on any other disorder for which occlusal modifications were performed was excluded from the study. Studies involving ICAGD as a treatment modality for any other disorder were excluded from the study. Studies in language other than English were excluded from the study. Studies without disclusion time measurement follow-up of 1 week, 1 month, 3 months and 6 months were excluded from the meta-analysis; however, included in the risk of bias assessment. The studies obtained by the mentioned search strategy were imported to a software program (Mendley software Verison 1.19.8) to remove duplicates. In Prisma flowchart, a descriptive summary of data selection has been put forth in the Figure 1.^[16]

The Methodologic quality of included reviews was investigated using Cochrane ROB 2 tool^[17] for randomized control trials, ROBINS-I^[18] for non-randomized trials, JBI checklist for case reports^[19] and New-Castle Ottawa for observational studies.^[20]

The ROB 2 tool consists of 7 domains structured in the form of several signalling questions. The seven domains for individually randomized trials (including cross-over trials) are: Random sequence generation, Allocation concealment, blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Selective reporting, and other bias. The response options for the signalling questions: Yes; Probably yes; Probably no; No; No information; A response of ‘Yes’ may be indicative of either a low or high risk of bias, depending on the most natural way to ask the question.

ROBINS-I tools (“Risk of Bias in Non-randomized Studies - of Interventions”) is concerned with evaluating the risk of bias (RoB) in the results of NRSIs that compare the health effects of two or more interventions. NRSIs are evaluated using this tool are quantitative studies estimating the effectiveness (harm or benefit) of an intervention, which did not use randomization to allocate units (individuals or clusters of individuals) to comparison groups. The ROBINS-I tool covers seven domains through which bias might be introduced into a NRSI. The first two domains address issues before the start of the interventions that are to be compared (“baseline”) and the third domain addresses classification of the interventions themselves. The other four domains address issues after the start of interventions. Every domain is consisting of signalling questions which help the reviewers classify the study as “low risk,” “moderate risk”, “critical risk” or “no information”.

JBI checklist’s purpose is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. It consists of 12 questions and the response option available are Yes, No, Unclear or Not/Applicable.

New-castle Ottawa checklist assess the methodological qualities of cohort observational studies. It consists of 8 questions for selection, comparability, and outcome. Three authors (S.K.K., A.M.G. and A.K.G.) independently reviewed the risk of bias of all the studies included in the systematic review based on the four domains (Table 3). The risk of bias summary and applicability concerns were graphically plotted. The software used for the graphical plotting was Review Manager (RevMan) 5.3 software version.

Meta-regression was used to determine clinical heterogeneity between the studies. Statistics for chronic myofascial pain such as disclusion time, frequency of pain symptoms, pain scale score and proportions were calculated and pooled quantitatively.

IV. Results

A total of 318 articles were identified after removing duplicates. Of the 318 articles 161 articles were excluded after screening the title. Thus, 157 articles were obtained after title screening. 68 articles were further excluded after abstract screening. 89 full text articles were available for full text screening, of which 63 articles were further excluded. After full text reading only 26 articles met the inclusion and exclusion criteria and thus were included for quality assessment and 5 articles were selected for meta-analysis.

Three reviewers (S.K.K. and A.M.G. and A.K.G.) independently extracted qualitative and quantitative data such as sample size, age, sex, method of intervention and disclusion time from the included studies.

Among the three RCTs^[21-23] included in the review, two showed high risk of bias and one study showed low risk. In study conducted by Thumati 2020^[23] and Thumati 2021^[22], information about blinding of personnel was not mentioned, leading to high risk of bias in these studies. All the included non-randomized studies^[11,24-35] showed moderate risk of bias as the information about selection of participants in to the studies was not mentioned. The risk of bias for three cohort observational studies was moderate while one showed low risk of bias. In observational studies by Thumati 2015^[36], Sutter 2020^[37] and Thumati 2021^[12], Ben 2021^[38] information about representativeness of cohort was not mentioned along with selection of non-exposed cohort which contributed to selection bias in these studies. Four case reports^[39-42] were included. All the case reports showed low risk implying high quality. None of the case reports reported adverse events in the case. Figure 2 and 3 depict risk of bias and applicability concern summary and graph.

A total of 1014 patients were evaluated for ICAGD treatment to reduce disclusion time (mean: 44.08 patients). The age range of included patients was 19-83 years (mean 32 years). Total of 514 females and 234 males were treated for chronic myofascial pain dysfunction. This shows a predilection of MPDS affecting young adults which seems to be more common among women than men.

Two studies (Thumati 2015, Thumati 2014) evaluated disclusion time on left and right side at Day 1, 1 month and 6 months follow-up, whereas three studies (Kerstein 1994, Thumati 2015, Thumati 2014) evaluated disclusion time on left and right side at 1 year follow-up period before and after treatment with ICAGD. The pooled mean difference for left side was 1.10 [0.99, 1.21] indicating that mean disclusion time was greater Pre-treatment as compared to post-treatment.

Two studies (Thumati 2020, Thumati 2021) evaluated pain scores at 1 week, 1 month, 3 months and 6 months interval between ICAGD group and control group. The pooled mean difference was -5.60[-6.96,-4.24] indicating that the pain scores were reduced in ICAGD group as compared to control group.

Two studies (Thumati 2020, Thumati 2021) evaluated frequency of pain symptoms at 1 week, 1 month, 3 months and 6 months interval between ICAGD group and control group. The pooled mean difference was -16.42[-38.19,5.35] indicating that the frequency of pain symptoms was reduced in ICAGD group as compared to control group. These results were statistically significant ($p<0.05$). As heterogeneity was greater than 50% ($I^2=100\%$), random effects model was used for meta-analysis (Supplementary Table 1,2,3 and 4).

V. Discussion

The present study reviewed the effectiveness of ICAGD in reducing disclusion time in patients with chronic myofascial pain dysfunction. The null hypothesis was rejected as there was found to be a significant difference in disclusion time in patients who were treated with ICAGD. The findings indicated that ICAGD serves as a profound treatment modality to reduce disclusion time in patients with chronic myofascial pain dysfunction. Some authors claim that painful, chronic, and dysfunctional TMD symptoms arise from both physiological causations, and emotional anxiety/depression precipitated by stressful events in patient's life. Several authors have reported a strong correlation between occlusal interferences and TMD, based on the rationale that occlusal disturbances lead to mandibular instability, and hence increase the activity of the masticatory muscles (for stabilizing the jaw), eventually leading to TMD.

Prolonged posterior tooth engagement of the occlusal surfaces of opposing maxillary and mandibular premolars and molars during excursions results in prolonged compressions of these same posterior teeth. These prolonged compressions activate the muscle fibres to contract for as long as the teeth remain compressed into their periodontal ligament while the occlusal surfaces are engaged. Shortening disclusion time to <0.5 seconds establishes an occlusal scheme where the posterior teeth compress each other and their respective periodontal ligament fibres for far less time than during the untreated or pre-treatment condition. The shortened PDL compression time shortens the contraction time of the muscles of mastication such that far less lactic acid accumulates within the muscle fibers and fascia. This makes it possible for the involved muscles to better clear the pre-existing lactic acid from the muscle thus ensuring re-oxygenation and limiting future ischemia. More muscle fibers of an individual muscle can then contract maximally.

A measurementdriven, computerguided occlusal adjustment procedure whose primary therapeutic goal of measurably decreasing the time required for all molars and premolars to disclude from each other in fractions of seconds during mandibular excursions, (known as disclusion time reduction; <0.4 s/excursion), has been shown to be successful in treating myofascial pain patients. The concept of treating the MPDS patients with

ICAGD is not new. Various studies have been performed in the past evaluating their effect on symptoms. A study by Kerstein in 1991, performed on seven female subjects with MPDS, and treated with ICAGD to reduce Disclusion Time to less than 0.4 seconds showed statistically significant changes pre- to post-treatment Disclusion Time and significant symptom resolution. Additionally, the same author showed that statistically significant muscle activity level reductions occurred in 45 symptomatic MPDS patients, when ICAGD was properly performed.

In a controlled occlusal adjustment study by Thumati et al.^[22] that compared treated, placebo, and untreated myofascial pain subject groups with respect to their differences in disclusion time, symptom remissions began in the treated group within 1 week after the disclusion time was reduced <0.4 s, and symptom resolution lasted for the 3year period of posttreatment observation. This study showed that multiple recall visit disclusion time means were statistically equivalent to the posttreatment day 1 disclusion time mean. Further, the standard deviations from recall visittovisit remained constant throughout the 3year period of observation. The mean differences also remained constant when a comparison between day 1 pre-treatment and subsequent visit measurements were made.

This suggests that once disclusion time is reduced <0.4 s, it is a lasting occlusal change. These findings are very similar to those of another disclusion time reduction study that verified that once the disclusion time was properly reduced, it remained constant, leading to the retention of proper, muscle function and low symptom appearances. Multiple published studies have shown that, due to prolonged disclusion time (> 0.5 s per excursion), masticatory muscle hyperactivity occurs during excursive movements that clinically present as commonly observed muscular TMD symptoms (jaw pain, chewing fatigue, facial tension, temporal headache, and some neck pain, clenching and grinding of teeth). This masticatory muscle hyperactivity during the resting state overworks the involved muscles into painful muscular fatigue, often being the prime causative agent for jaw symptoms, headaches, and facial tension. After ICAGD shortens the disclusion time to < 0.5 s per excursion, the muscle hyperactivity is minimized to near resting state values with symmetry, synergy, and timing, which then improves oxygenation of the involved muscles, improves muscular function, and chronic symptoms lessen.

Our results highlight the role of the damaging inputs to the neuromuscular system from the lengthy posterior occlusal contacts during protrusive excursions and the unbalanced occlusal forces in the aetiology of chronic myofascial pain in dentate adults. Relief was reported to be immediate, but became more pronounced after a waiting period of about 4-8 weeks. The sequence of occlusal adjustments was focused on establishing an immediate posterior disclusion for mandibular protrusive movements from the habitual closure position of the jaw, without refining the centric relation occlusion.

VI. Conclusion

Based on the findings of this systematic review and meta-analysis, the following conclusions were drawn:

1. ICAGD can be employed in patients with chronic myofascial pain dysfunction to reduce disclusion time to relieve the painful symptoms of the disease.
2. Symptoms like functional restrictions, jaw stiffness, headaches, earache, and the resultant levels of emotional depression from living with chronic painful symptoms, were all dramatically improved within the treatment group within weeks making it a successful treatment modality to be taken into consideration.
3. The evidence acquired needs to be standardized and further research is required on the subject to provide stronger evidence.

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Tables

Table 1. PICOS elements

Elements	Contents
Population	Studies included patients with chronic myofascial pain dysfunction
Intervention	Immediate complete anterior guidance development
Comparison	Occlusal equilibrium or none
Outcome	Disclusion time reduction
Study design	In-vivo studies

PICOS,
Population, Intervention, Comparison, Outcome, and Study design.

Table 2. Adopted keyword and electronic search strategies

Population	“Chronic myofascial pain dysfunction syndrome*”[tiab] OR “Myofascial pain dysfunction*”[tiab] OR myofascial pain*”[tiab] OR “Chronic myalgic temporomandibular joint dysfunction (TMD) symptoms*”[tiab] OR “Occluso-muscular disorder OR muscularly symptomatic*”[tiab] OR “Chronic occluso-muscle disorder*”[tiab] OR “Chronic Pain Symptom*”[tiab] OR “Temporomandibular disorders*”[tiab] OR “Myofascial pain symptomatic patients*”[tiab]
Intervention	“Immediate Complete Anterior Guidance Development*”[tiab] OR “Computer-guided occlusal adjustment procedure*”[tiab] OR “ICAGD*”[tiab]
Comparison	“Occlusal Adjustment*”[tiab] OR “Occlusal Equilibration*”[tiab]
Outcome	“Reduction in disclusion time*”[tiab] OR “Disclusion time*”[tiab] OR “Reduced disclusion time*”[tiab] OR “Shortening disclusion time*”[tiab] OR “Shortened disclusion time*”[tiab] OR “Disclusion Time Reduction*”[tiab]
Combined search	“Chronic myofascial pain dysfunction syndrome*”[tiab] OR “Myofascial pain dysfunction*”[tiab] OR myofascial pain*”[tiab] OR “Chronic myalgic temporomandibular joint dysfunction (TMD) symptoms*”[tiab] AND “Immediate Complete Anterior Guidance Development*”[tiab] OR “Computer-guided occlusal adjustment procedure*”[tiab] OR “ICAGD*”[tiab] AND “Occlusal Adjustment*”[tiab] OR “Occlusal Equilibration*”[tiab] AND “Reduction in disclusion time*”[tiab] OR “Disclusion time*”[tiab] OR “Reduced disclusion time*”[tiab] OR “Shortening disclusion time*”[tiab] OR “Shortened disclusion time*”[tiab] OR “Disclusion Time Reduction*”[tiab]

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Studies including participants of any age and gender diagnosed with Chronic Myofunctional pain dysfunctional syndrome (MPDS) and Temporomandibular disorders (TMDs). Studies including participants treated using Immediate Complete Anterior Guidance Development (ICAGD) and other treatments for chronic MPDS for disclusion time reduction. Studies published in English language only. Human studies. Studies published from 1 st January 1980 to 1 st January 2023 RCTs or quasi experimental studies, non-randomized trials, longitudinal studies, cross-sectional studies, case reports, case series. Studies with full-text articles were be included.
Exclusion criteria	Studies involving patients not providing informed consent. Clinical trials or In-vivo studies on any other temporomandibular disorder. Surveys and Questionnaire Based studies. Review letters, personal opinions, book chapters and conference abstracts. Articles published in languages other than English.

Figure 1. PRISMA flowchart

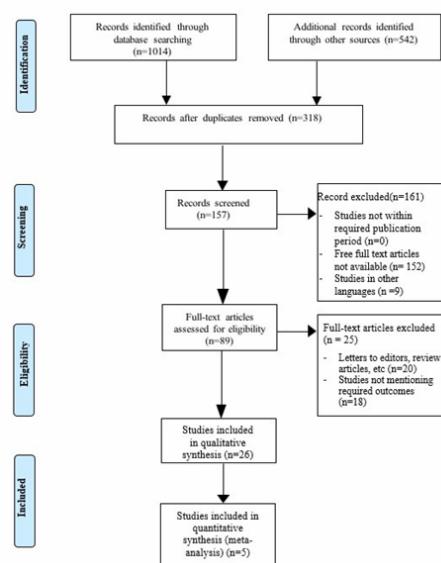


Figure 2. ROB for RCT

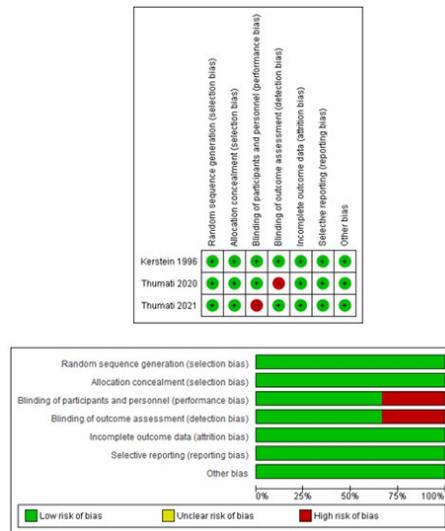


Figure 3. ROB for non-RCT

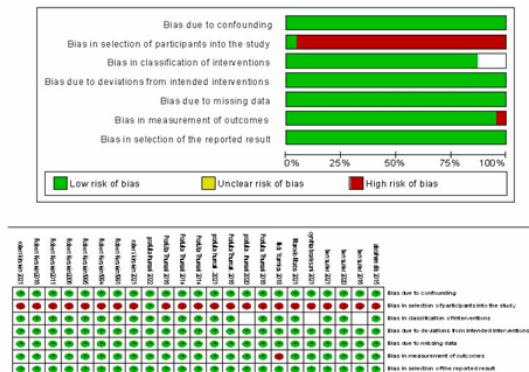


Figure 4.

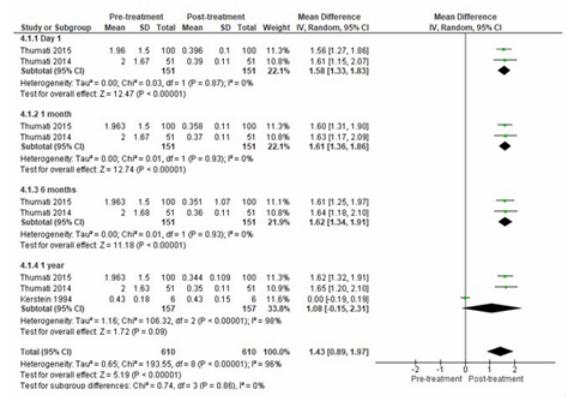


Figure 5.

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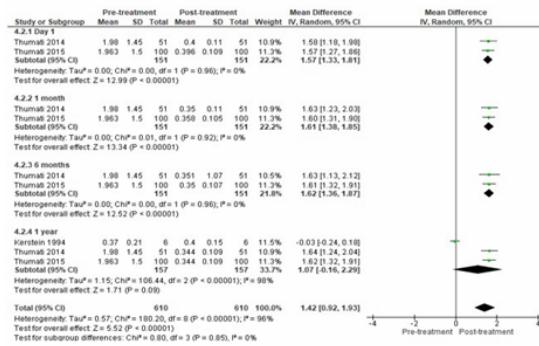


Figure 6.

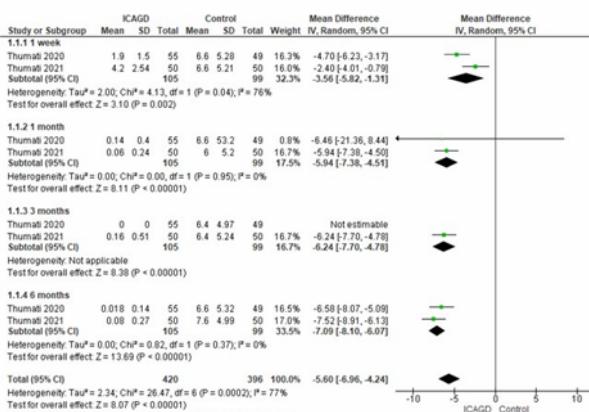
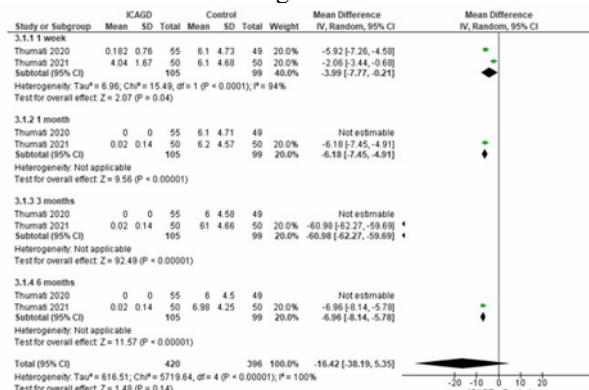


Figure 7.



Supplementary tables

Supplementary table no.1. ROB-2 checklist to assess quality of included RCT'S

Serial No.	Author (Year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants	Blinding of personnel/care provider (Performance bias)	Blinding of outcome (Detection bias)	Incomplete outcome data (attrition bias)	Selective Reporting (Reporting bias)	Other bias	Risk of bias
1	Kerstein 1996	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
2	Thumati 2020	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate risk	High risk
3	Thumati 2021	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate risk	High risk

Supplementary table no.2. ROBINS-I checklist to assess quality of included non-RCT'S

Serial no.	Author (Year)	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended	Bias due to missing data	Bias in measurement of outcome	Bias in selection of the reported result	Risk of bias

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			into the study		interventions		s		
1	Kerstein 1991	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
2	Kerstein 1994	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
3	Kerstein 1995	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
4	Kerstein 2006	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
5	Kerstein 2011	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
6	Thumati 2014	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
7	Dib 2015	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
8	Thumati 2016	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
9	Kerstein 2016	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
10	Thumati 2018	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
11	Yiannios 2018	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
12	Matos 2021	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
13	Kirstein 2021	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
14	Kirstein 2021	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
15	Thumati 2022	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk

Supplementary table no.3. New-Castle Ottawa checklist to assess quality of included observational studies

Serial No.	Author (Year)	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the study	Comparability of cohorts on the basis of design	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score	Risk of bias
1	Thumati 2015	-	-	*	*	NA	*	*	*	5	Moderate
2	Sutter 2020	-	-	*	*	NA	*	*	*		Moderate
3	Thumati 2021	-	-	*	*	NA	*	*	*	5	Moderate
4	Ben 2021	*	*	*	*	NA	*	*	*	7	Low

Supplementary table no.4. JBI checklist to assess quality of included case reports

Serial No.	Author (Year)	Demographic Characteristics	Patient History	Clinical Presentation Of condition	Diagnostic Tests used	Treatment Procedures Description	Post intervention Clinical Condition	Adverse Events	Takeaway Lessons	Total
1	Sutter 2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
2	Thumati 2016	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
3	Thumati 2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
4	Brattesani 2021	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7