

Comparative safety and efficacy of percutaneous approaches for the treatment of trigeminal neuralgia: A systematic review and meta-analysis



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ABSTRACT

Percutaneous treatments for trigeminal neuralgia (TN) include glycerol rhizotomy (GR), radiofrequency thermocoagulation (RF), and balloon compression (BC), which aim to provide pain relief by targeted injury to the trigeminal nerve pain fibers. All three techniques are well established and can provide immediate pain relief; however each of them can be associated with a range of complications. Our objective was to compare the safety and efficacy of GR, RF and BC in patients with TN. This study was performed according to the PRISMA guidelines. A random effects model meta-analysis was conducted. Fourteen studies were included. The comparisons of RF vs GR comprised 2,518 patients overall. RF was associated with statistically significant higher odds of immediate pain relief (OR: 2.65; 95% CI: 1.29–5.44; I^2 :85.5%) when compared to GR. Patients in the RF group had a statistically significant higher risk of anesthesia in the trigeminal distribution (OR: 4.73; 95% CI: 2.25–9.96; I^2 :0%) and lower risk for herpes eruption (OR: 0.30; 95% CI: 0.17–0.56; I^2 :0%). The comparison of BC vs GR included 961 patients. Patients in the BC group had a statistically significant higher risk of mastication weakness (OR: 9.29; 95% CI: 2.71–31.86; I^2 :0%) and diplopia due to CN IV or CN V palsy (OR: 6.31; 95% CI: 1.70–23.33; I^2 :0%) compared to patients in the GR group. The comparisons of BC vs RF comprised 3,183 patients and did not show significant differences between the two groups. RF is associated with statistically significant higher odds for immediate pain relief and anesthesia and lower risk for post-operative herpes eruption as compared to GR. Patients in the BC group had a statistically significant higher risk to develop post-operative mastication weakness and diplopia when compared to GR.

1. Introduction

Trigeminal neuralgia (TN) is a neuropathic pain syndrome which affects the trigeminal nerve. [1] It is characterized by severe electric shock-like painful episodes in one or more divisions of the trigeminal nerve [1]. The annual incidence of TN is estimated between 4.3 and 27 per 100,000 population [2–4]. The first-line treatment of TN commonly involves medical management with use of analgesic and/or anti-epileptic drugs. However, TN can be refractory to pharmacotherapy which necessitates the utilization of various invasive or minimally invasive procedures [5].

The neurosurgical armamentarium for the management of refractory TN consists of major procedures including microvascular decompression (MVD), minimally invasive percutaneous treatments, and radiosurgery. [5] Even though MVD is associated with a well-established

efficacious profile and long-term analgesia, a number of patients will eventually need to undergo a percutaneous treatment for TN [6]. This is commonly the case for elderly patients or patients with comorbidities who are not good craniotomy candidates or patients with recurrent TN following MVD [7]. Importantly, percutaneous approaches have also been used as the first neurosurgical strategy by several centers [7–9].

Percutaneous treatments for TN include glycerol rhizotomy (GR), radiofrequency thermocoagulation (RF), and balloon compression (BC), all of which aim to provide pain relief by targeted injury to the trigeminal nerve pain fibers. All three techniques are considered simple and can provide immediate pain relief; however each of them has different selectivity of trigeminal divisions and can be associated with a range of complications. [10] Studies comparing the percutaneous treatment modalities often show conflicting results [11,12]. The aim of

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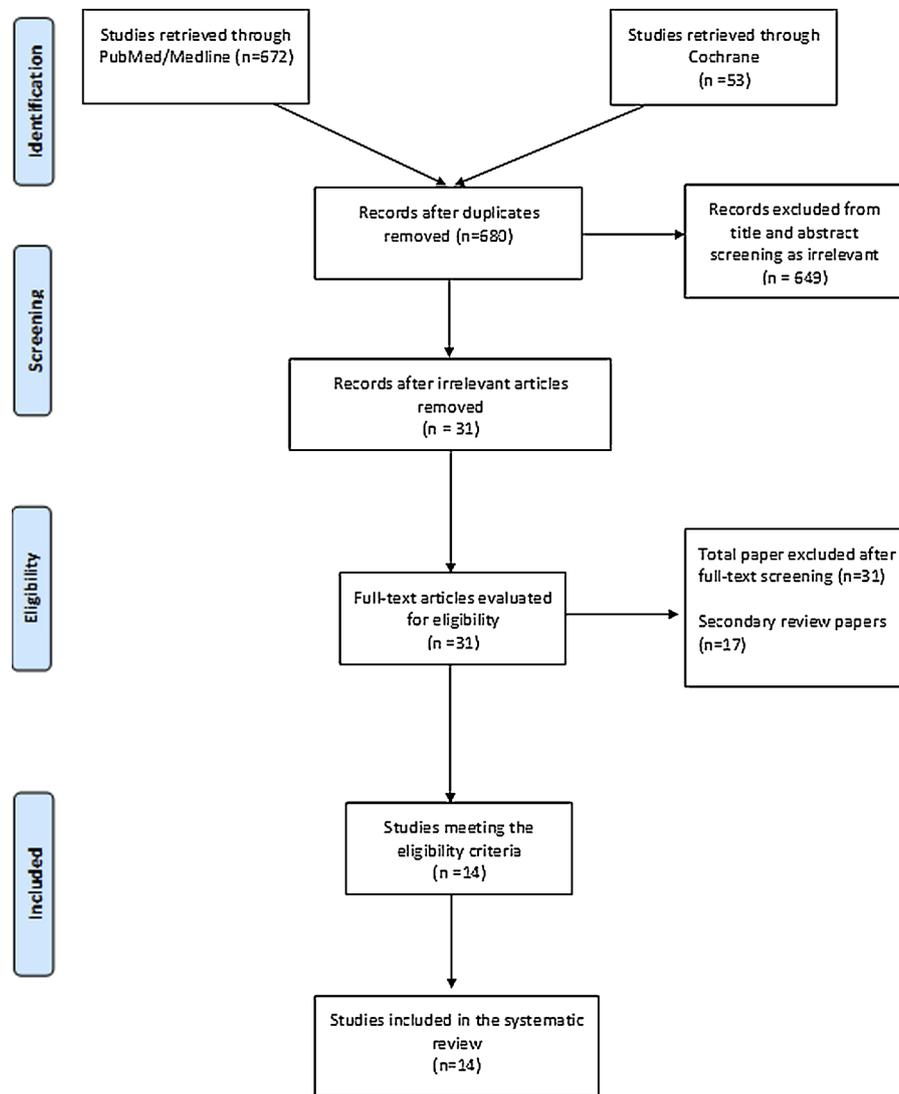


Fig. 1. Search PRISMA flow diagram.

this systematic review and meta-analysis was to synthesize all available outcomes from studies evaluating the comparative safety and efficacy of GR, RF and BC.

2. Materials and methods

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. [13]

2.1. Search strategy and selection criteria

Systematic searches were conducted in PubMed/Medline and Cochrane. The keywords used for PubMed were: glycerol, glycerolization, radiofrequency, thermorhizotomy, thermocoagulation, percutaneous balloon compression, microcompression, percutaneous compression and trigeminal neuralgia. The search was conducted by two independent investigators (PT, DX). Any disagreements or discrepancies were resolved by consensus.

A study was included in this meta-analysis if it fulfilled three predefined criteria: i) randomized controlled trials (RCT) or prospective and retrospective observational analyses comparing at least two of the following procedures: GR, RF or BC; ii) studies that reported

quantitative data on clinical outcomes of interest; and iii) studies published up to February 2019.

2.2. Data extraction and outcomes

Two reviewers, blind to each other (PT, DX), independently extracted the relevant data from the eligible studies. Variables abstracted were: first author, year of publication, years of enrollment, country, design of study, study arms, number of patients, age, gender, pain distribution, previous treatments for TN management, percentage of patients with multiple sclerosis (MS), percentage of patients with post-herpetic TN, duration of follow-up, immediate and delayed pain relief, pain recurrence, hypoesthesia, analgesia, dysesthesia, mastication weakness, keratitis, diplopia, hearing loss, cranial nerve palsy, herpes zoster eruption, numbness and meningitis. All disagreements were resolved following discussion and final decision was reached by consensus. The primary outcome was immediate pain relief which was defined as pain relief with or without analgesic medication following the procedure. Secondary outcomes were complication rates.

2.3. Risk of bias assessment

Risk of bias was assessed by one investigator (PT) with the Robins-I

Table 1
Important baseline study and patient characteristics.

Study	Treatment arms	N of patients	Age per group	Female gender, %	MS patients % per group	Previous failed percutaneous approach per group, N	Pain distribution, %						
							V1	V2	V3	V1 + V2	V2+V3	V1 + V3	V1 + V2+V3
Lee 1998	GR	36	-	-	-	-	-	-	-	-	-	-	-
	RF	235	-	-	-	-	-	-	-	-	-	-	-
Udupi 2012	GR	40	53.7	47.5	-	0	0	5	32	20	35	3	5
	RF	39	51.9	38.5	-	0	0	5.1	17.9	23	38.5	5.1	10.3
Bender 2013	GR	478	58.5	67	4	14	-	-	-	-	-	-	-
	RF	332	61.5	66	14	245	-	-	-	-	-	-	-
Haridas 2008	GR	147	67.6	58	-	-	-	-	-	-	-	-	-
	RF	145	70.2	58	-	-	-	-	-	-	-	-	-
Tan 1995	GR	50	69.8	64	-	0	-	-	-	-	-	-	-
	RF	80	62.1	63	-	0	-	-	-	-	-	-	-
Fraioli 1989	BC	159	-	-	1.8	13	-	-	-	-	-	-	-
	GR	32	-	-	6.25	5	-	-	-	-	-	-	-
	RF	533	-	-	3.3	25	-	-	-	-	-	-	-
Mohammad 2013	BC	19	-	-	100	0	-	-	-	-	-	-	-
	GR	39	-	-	100	-	-	-	-	-	-	-	-
	RF	6	-	-	100	-	-	-	-	-	-	-	-
Noorani 2016	BC	86	67.8	64.7	-	41	1.2	14.8	27.2	18.5	24.7	0	13.6
	GR	152	69.9	60.5	-	-	8.3	9	15.2	23.4	25.5	0	18.6
	RF	155	72.3	56.1	-	-	2.6	19.5	27.9	5.8	38.3	0	5.8
Asplund 2016	BC	82	71.5	53	20	-	21	51	28	-	-	-	-
	GR	124	68.7	74	12	-	7	75	18	-	-	-	-
Kouzounias 2010	BC	40	70	57	28	37	26	74	72	-	-	-	-
	GR	92	70	63	13	51	35	87	49	-	-	-	-
Mallory 2012	BC	69	62.8	67	100	60	3	10	25	7	52	3	0
	GR	67	60.5	55	100	35	0	12	31	5	43	9	0
Broggi 1993	BC	206	-	-	-	0	-	-	-	-	-	-	-
	RF	1000	-	-	-	0	-	-	-	-	-	-	-
Meglio 1989	BC	74	-	-	-	0	-	-	-	-	-	-	-
	RF	33	-	-	-	0	-	-	-	-	-	-	-
Frank 1989	BC	212	-	-	-	0	-	-	-	-	-	-	-
	RF	700	-	-	-	0	-	-	-	-	-	-	-

*BC: Balloon compression; GR: glycerol rhizotomy; RF: radiofrequency thermocoagulation; N: number; MS: multiple sclerosis, “-”: indicates data not reported.

Table 2
Procedural details reported by the included studies.

Study	Balloon Compression-Compression time	Glycerol Rhizolysis - Dose	Radiofrequency Thermocoagulation
Lee 1998	-	0.3 ml	- 5 lesions for 60 sec -1 st lesion at 60 °C -Next at 70 °C-80 °C
Udupi 2012	-	0.3 ml	- 5 lesions for 60 sec -1 st lesion at 60 °C -Next at 70 °C-80 °C
Bender 2013	-	0.3-0.4 ml	60 °C for 60 sec
Haridas 2008	-	0.4-0.8 ml	70 °C for 60 sec
Tan 1995	-	0.2-0.4 ml	70 °C for 60sec
Fraoli 1989	3-10 min (majority for 5-7 min)	0.2-0.4 ml	47-108 °C
Mohammad 2013	60 sec ^a	0.5 ml	NR
Noorani 2016	60 sec x3 times	0.36 ml	60-80 °C for 60sec
Asplund 2016	90-180 sec	-	-
Kouzounias 2010	60-120 sec	-	-
Mallory 2012	60-300sec	-	-
Broggi 1993	-	-	-
Meglio 1989	-	-	-
Frank 1989	-	-	-

* For repeated procedures, each extra compression was extended for 30 sec for each previous lesion; NR: not reported.

tool for non-randomized studies. [14] The following domains for the non-randomized studies were evaluated: confounding, selection of participants, departure from intended interventions, missing data, measurement of outcomes and selective reporting.

2.4. Statistical synthesis and analysis

Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were used for the outcomes. A random effects model was used to account for heterogeneity among studies. Heterogeneity was assessed with the Higgins I-square statistic. [15] I² greater than 50% indicated significant heterogeneity. [15] Funnel plots for the evaluation of publication bias were not created as none of the outcomes were synthesized

by more than ten studies [16]. Forest plots were used to graphically display the effect size in each study and the pooled estimates. A p-value of < 0.05 was considered significant. STATA 14.1 (StataCorp, College Station, Texas) statistical software was used for all analyses.

3. Results

3.1. Search results

The literature search yielded 680 articles after duplicates were removed. Following full-text evaluation, 14 articles met the pre-determined search criteria and were included in this meta-analysis as shown in the PRISMA flow diagram (Fig. 1).

Table 3
Relative frequencies of all available outcomes in each group.

Outcome	RF vs GR (%)	BC vs GR (%)	BC vs RF
Immediate pain relief	88.3 vs 72.8*	79.1 vs 63.4	81.9 vs 92.7
Pain recurrence	28.5 vs 43.2	23.7 vs 43.8	22.8 vs 17.4
Anesthesia	18.2 vs 30.4*	NR	NR
Herpes eruption	2.4 vs 8*	5.2 vs 6.5	NR
Anesthesia dolorosa	0.75 vs 0.29	0.4 vs 0.2	0.4 vs 1.3
Dysesthesia	4.7 vs 2.5	6.6 vs 10.7	10.3 vs 8
Hypoesthesia	93.5 vs 94.5	68.6 vs 45.5	
Paresthesia	8.9 vs 3.2	8.1 vs 4.3	8.1 vs 12.9
Reduced corneal reflex/keratitis	12.5 vs 4.8	4.9 vs 6.5	NR
Mastication weakness	1.1 vs 0.3	6.3 vs 0*	7.1 vs 5.3
Diplopia	NR	4 vs 0.4*	1.3 vs 0.2
Numbness	NR	18 vs 59.6	NR

* designates statistical significance.

3.2. Characteristics of the included studies

All 14 studies were retrospective observational real-world studies. None of the included studies were assessed as having serious risk of bias. A detailed evaluation of risk of bias is summarized in **Supplementary Table 1**. The evaluation of publication bias was not feasible as none of the outcomes of interest were synthesized by more than ten studies. [16] Important study and baseline patient characteristics are presented in **Table 1**. Three of the included studies reported a comparison of all three different percutaneous approaches. [17–19] Five studies [20–24] compared RF vs GR while three studies [11,12,25] compared BC vs GR and three studies [26–28] compared BC vs RF. Procedural characteristics including duration of compression in the BC studies, temperature and duration in the RF studies and dose of injected glycerol in the GR studies are summarized in **Table 2**. **Table 3** summarizes the rates of outcome occurrence in each group for all available outcomes.

3.2.1. Radiofrequency thermocoagulation (RF) vs glycerol rhizotomy (GR)

Eight studies were synthesized for the comparison between BC and

RF comprising 2518 patients overall (RF: 1530, GR: 988). [17–24] RF was associated with statistically significant higher odds of immediate pain relief (OR: 2.65; 95% CI: 1.29-5.44; I²:85.5%) when compared to GR (**Fig. 2**). The rates of pain recurrence during the mean long-term follow-up (5-30 months) were similar between the two groups (OR: 0.81; 95% CI: 0.48-1.37; I²:80.7%) (**Fig. 3**). Patients in the RF group had a statistically significant higher risk of anesthesia in the trigeminal distribution (OR: 4.73; 95% CI: 2.25-9.96; I²:0%) (**Fig. 4**) and lower risk for herpes eruption (OR: 0.30; 95% CI: 0.17-0.56; I²:0%) (**Fig. 5**). The rates of anesthesia dolorosa (OR: 2.11; 95% CI: 0.42-10.51; I²:0%), dysesthesia (OR: 1.62; 95% CI: 0.85-3.09; I²:0%), hypoesthesia (OR: 4.94; 95% CI: 0.35-69.29; I²:93.8%), paresthesia (OR: 1.10; 95% CI: 0.52-2.33; I²:22.9%), reduced corneal reflex or keratitis (OR: 1.33; 95% CI: 0.62-2.81; I²:51.4%) and mastication weakness (OR: 2.14; 95% CI: 0.09-48.96; I²:63.4%) were similar between the RF and GR groups.

3.2.2. Balloon compression (BC) vs glycerol rhizotomy (GR)

Six studies were synthesized for the comparison between BC and GR including in total 961 patients (BC: 455, RF: 506). [11,12,17–19,25], The rates of immediate pain relief (OR: 2.31; 95% CI: 0.94-5.70; I²:85.4%) (**Fig. 6**) and pain recurrence during the mean long-term follow-up (6-28.5 months) (OR: 0.52; 95% CI: 0.23-1.21; I²:80.2%) (**Fig. 7**) were similar between the BC and GR groups. Patients in the BC group had a statistically significant higher risk of mastication weakness (OR: 9.29; 95% CI: 2.71-31.86 ; I²:0%) (**Fig. 8**) and diplopia due to CN IV or CN V palsy (OR: 6.31; 95% CI: 1.70-23.33; I²:0%) (**Fig. 9**) compared to patients in the GR group. Other post-operative complication rates including anesthesia dolorosa (OR: 0.68; 95% CI: 0.05-10.14 ; I²:38.3%), dysesthesia (OR: 0.71; 95% CI: 0.21-2.42; I²:73.2%), hypoesthesia (OR: 2.35; 95% CI: 0.86-6.45; I²:81.7%), paresthesia (OR: 1.64; 95% CI: 0.35-7.59; I²:67.5%), numbness (OR: 0.60; 95% CI: 0.00-125.96; I²:97.9%), herpes eruption (OR: 0.84; 95% CI: 0.40-1.78; I²:0%) and reduced corneal reflex or keratitis (OR: 0.73; 95% CI: 0.33-1.59; I²:0%) were similar between the BC and GR groups.

3.2.3. Balloon compression (BC) vs radiofrequency thermocoagulation (RF)

Six studies were synthesized for the comparison between BC and RF

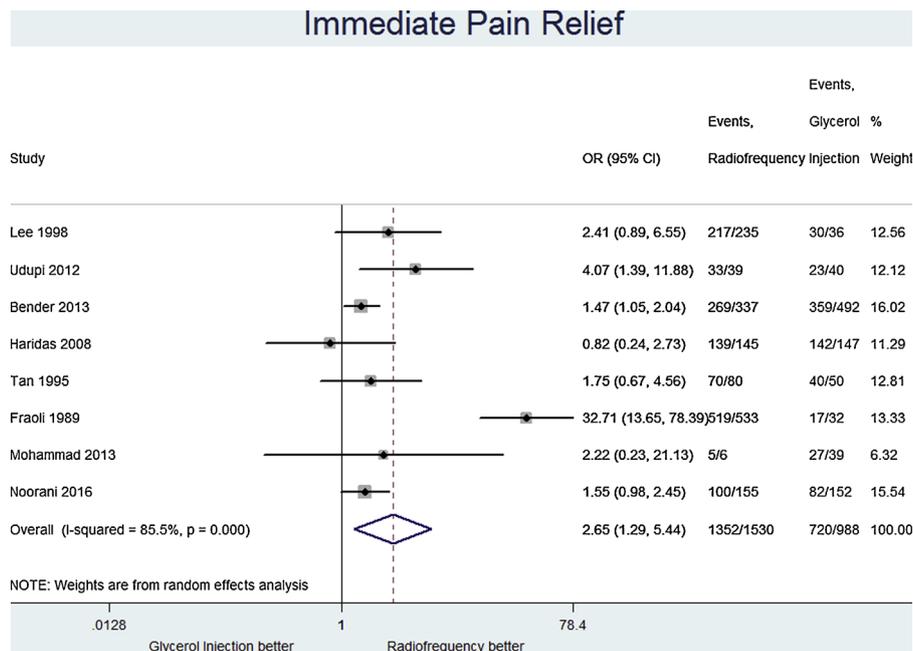


Fig. 2. Forest plot comparing radiofrequency thermocoagulation vs. glycerol rhizotomy in terms of immediate pain relief.

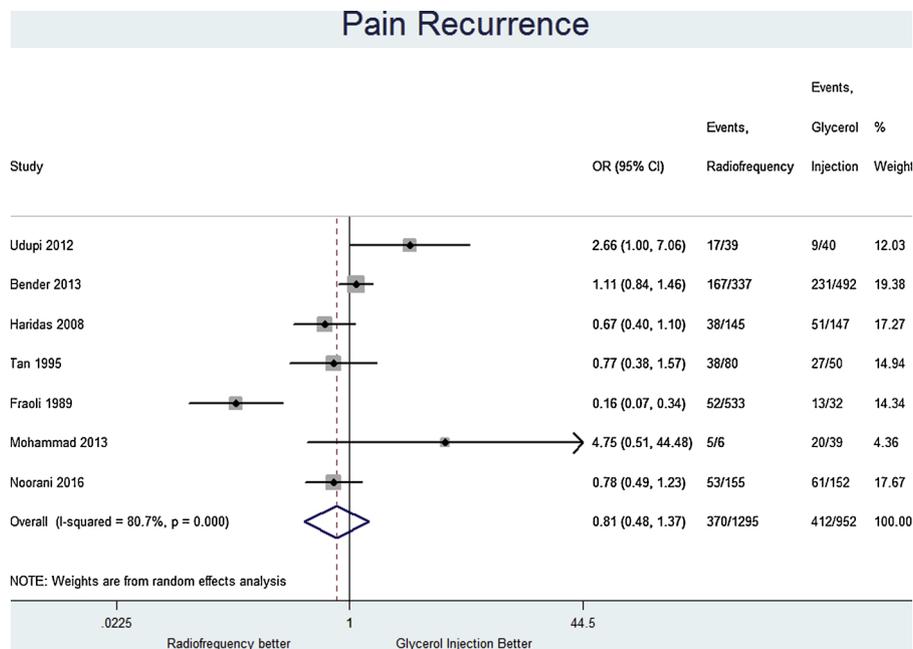


Fig. 3. Forest plot comparing radiofrequency thermocoagulation vs. glycerol rhizotomy in terms of pain recurrence.

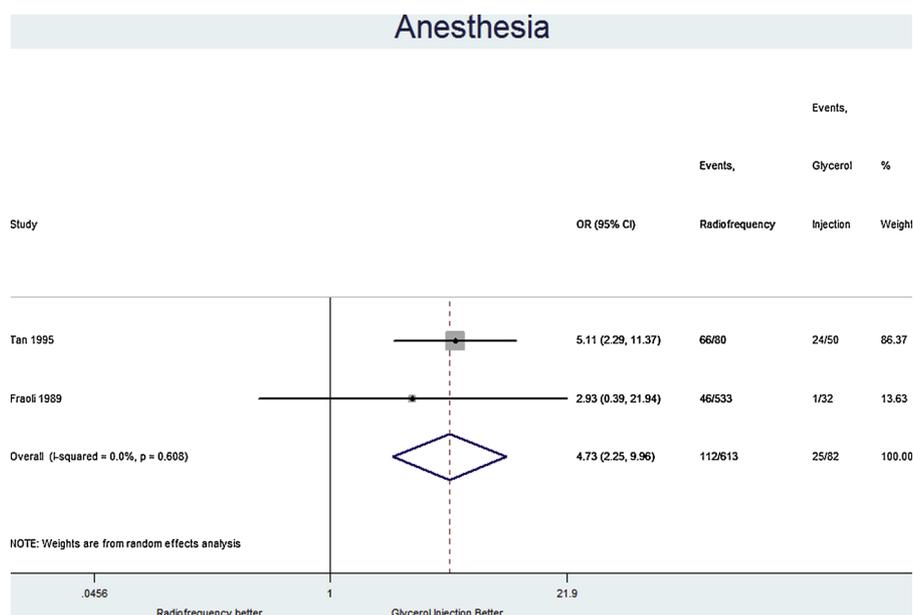


Fig. 4. Forest plot comparing radiofrequency thermocoagulation vs. glycerol rhizotomy in terms of post-operative anesthesia at the trigeminal nerve region.

comprising 3183 patients overall (BC: 756, RF: 2427). [17–19,26–28], No differences between the two approaches were identified in terms of immediate pain relief (OR: 0.63; 95% CI: 0.23–1.74; I²:87.5%) (Fig. 10) or pain recurrence during the mean long-term follow-up (5–29 months) (OR: 0.72; 95% CI: 0.35–1.47; I²:81.5%) (Fig. 11). The rates of anesthesia dolorosa (OR: 0.46; 95% CI: 0.08–2.66; I²:0%), cranial nerve IV palsy (OR: 4.95; 95% CI: 0.90–27.19; I²:0%), dysesthesia (OR: 0.83; 95% CI: 0.32–2.12; I²:76.5%), mastication weakness (OR: 1.69; 95% CI: 0.76–3.75; I²:57.8%) and paresthesia (OR: 0.90; 95% CI: 0.18–4.55; I²:86.5%) were similar between the two groups.

3.3. Subgroup analyses with multiple sclerosis (MS) patients

Subgroup analyses including only MS patients were conducted. The rates of immediate pain relief was higher in the RF group (63/

74 = 85.1%) compared to the GR group (42/63 = 66.6%); however statistical significance was not reached (OR: 4.13; 95% CI: 0.60–28.26; I²:55.1%) (Fig. 12). No differences were identified in terms of immediate pain relief for the comparison of BC vs GR (OR: 1.82; 95% CI: 0.23–14.6; I²:69.6%) and BC vs RF (OR: 0.26; 95% CI: 0.00–52.19; I²:81.6%) (Fig. 13).

The rates of pain recurrence was similar between the RF and GR groups (OR: 2.67; 95% CI: 0.42–17.08; I²:0%), BC vs GR (OR: 1.40; 95% CI: 0.49–4.04; I²:0%), and BC vs RF (OR: 2.04; 95% CI: 0.03–148.53; I²:76.5%).

4. Discussion

This is the first meta-analysis synthesizing all published studies comparing the percutaneous approaches currently available for the

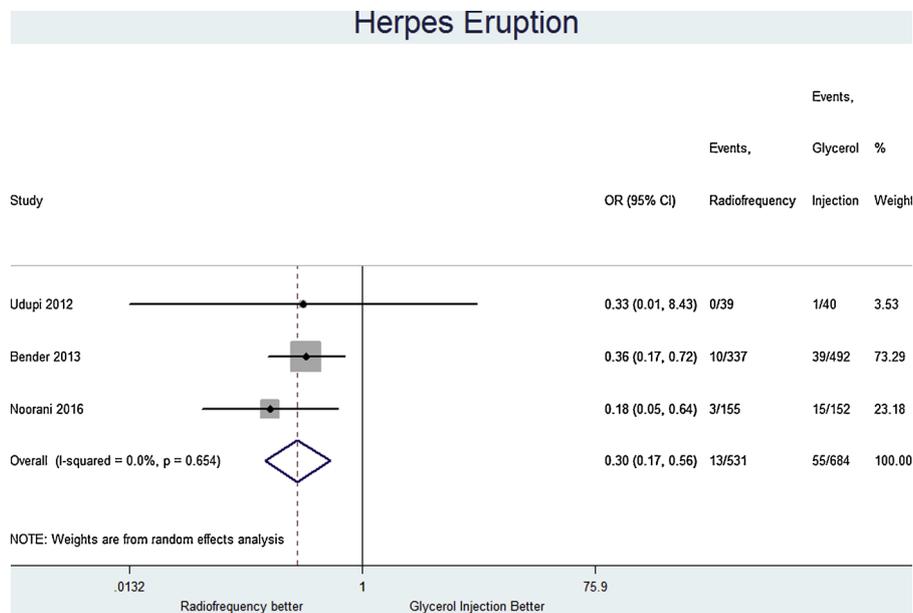


Fig. 5. Forest plot comparing radiofrequency thermocoagulation vs. glycerol rhizotomy in terms of herpes eruption.

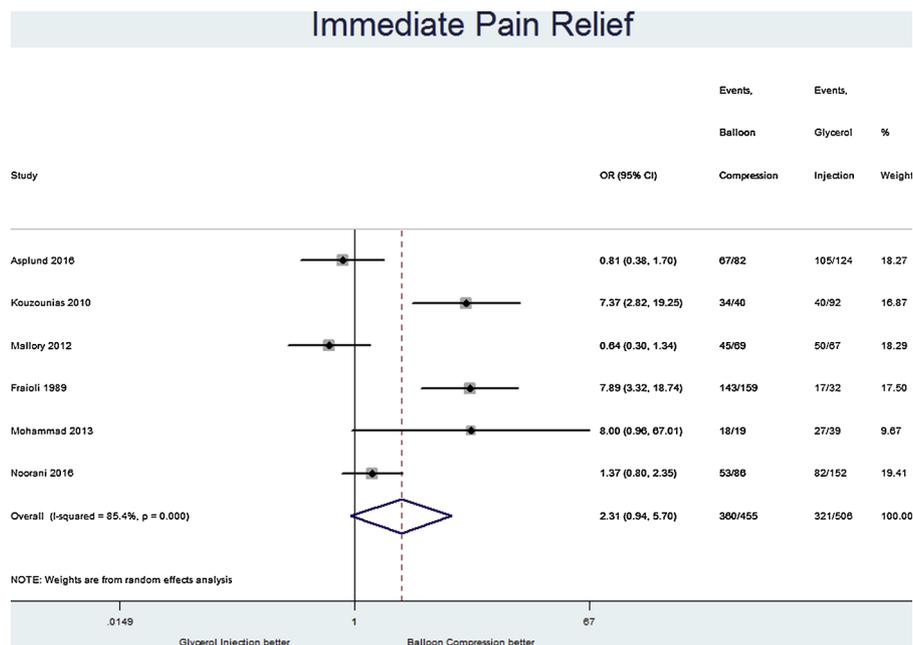


Fig. 6. Forest plot comparing balloon compression vs. glycerol rhizotomy in terms of immediate pain relief.

treatment of TN. Our study showed that RF is associated with statistically significant higher odds for immediate pain relief when compared to GR; however, this was accompanied by a significantly higher risk for anesthesia in the trigeminal distribution. GR was associated with a statistically significant lower risk for post-operative herpes eruption as compared to RF. Other post-operative complications were similar between the RF and GR groups. Patients in the BC group had a statistically significant higher risk to develop post-operative mastication weakness and diplopia due to cranial nerve IV or VI palsy when compared to GR. No other differences were detected between the BC and GR groups. In addition, the comparison of BC and RF did not show any statistically significant differences in terms of safety and efficacy outcomes.

Initial pain relief and pain recurrence are the defining factors of efficacy for the three percutaneous procedures. [1] RF demonstrated

statistically significant higher pain relief rates compared to GR. Notably, RF has the advantage of selective lesioning of individual trigeminal nerve branches [10]. Several comparative studies had showed a trend for superior pain relief in patients who had RF as compared to GR without reaching statistical significance [17,21]. Synthesis of all available studies increased the sample size and statistical power allowing for the detection of a statistically significant difference between RF and GR. A possible explanation could be that RF provides the opportunity for pre-ablative testing with sensory stimulation and increased mapping accuracy, which in turn, allows for targeted lesions with immediate patient feedback. [29,30] However, this comparison was associated with a high amount of heterogeneity ($I^2 : 85.5\%$). This could be explained by the inconsistency between the results reported by individual studies along with the experience of the operator and

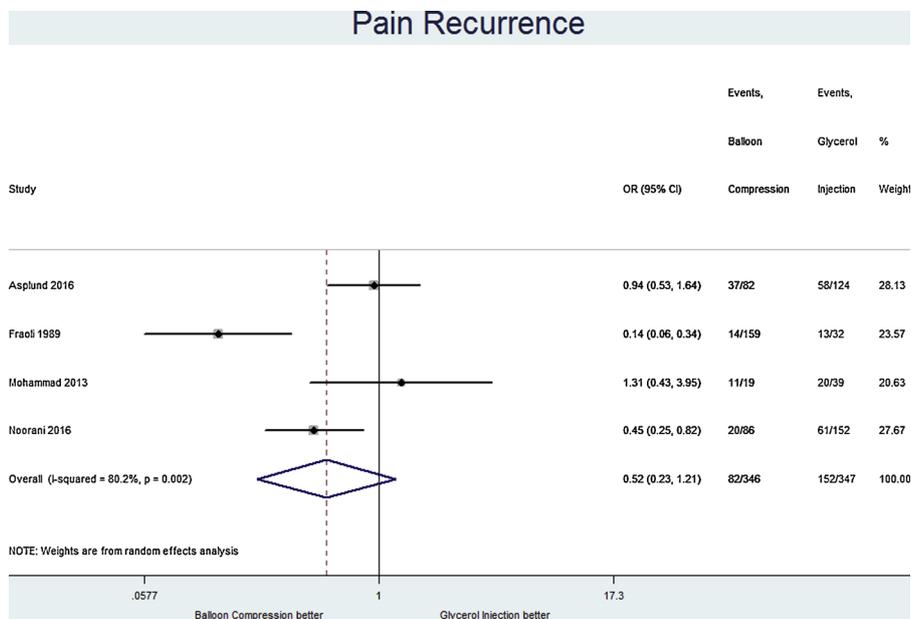


Fig. 7. Forest plot comparing balloon compression vs. glycerol rhizotomy in terms of pain recurrence.

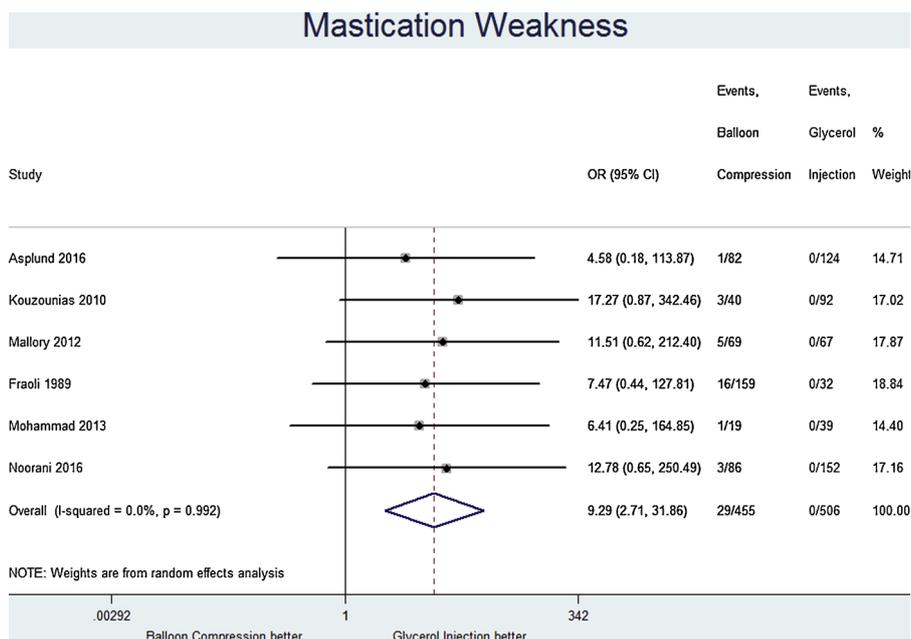


Fig. 8. Forest plot comparing balloon compression vs. glycerol rhizotomy in terms of post-operative mastication weakness.

differences between the temperature and duration of the radio-frequency current. It should be noted, however, that pain recurrence was similar in the RF and GR groups during the long-term follow-up. In contrast, RF was associated with an increased risk to develop anesthesia compared to GR, which was defined as complete sensory loss (RF: 112/613 = 18.2% vs GR: 25/82 = 30.4%); however this outcome was only synthesized by two studies which limits its generalizability [18,24]. Tan et al. reported a significantly increased post-operative sensory loss in the distribution of the trigeminal nerve in patients who had RF compared to GR (82.5% vs 48%). [24] It has been already suggested that RF, in general, can cause substantial sensory loss.[18] Importantly, neurophysiologic studies reported that this complication may show only slight recovery [31].

One of the novel findings of the present study is the statistically significant 9-fold increase in the risk to develop mastication weakness following BC as compared to GR. None of the individual included studies was able to show a statistically significant difference between the two percutaneous strategies. The present study synthesized all available data and demonstrated that 6.3% (29/455) and 0% (0/506) in the BC and GR groups respectively induced mastication weakness. However, clinically significant deficits are rare and the majority of cases regress spontaneously within a few weeks. [11,12] In addition, the risk of diplopia due to cranial nerve lesions to the IV and VI nerves demonstrated a statistically significant increase in the BC (11/277 = 4.8%) versus the GR group (2/435 = 0.45%). Similarly, none of the individual studies included in this comparison showed a statistically significant difference

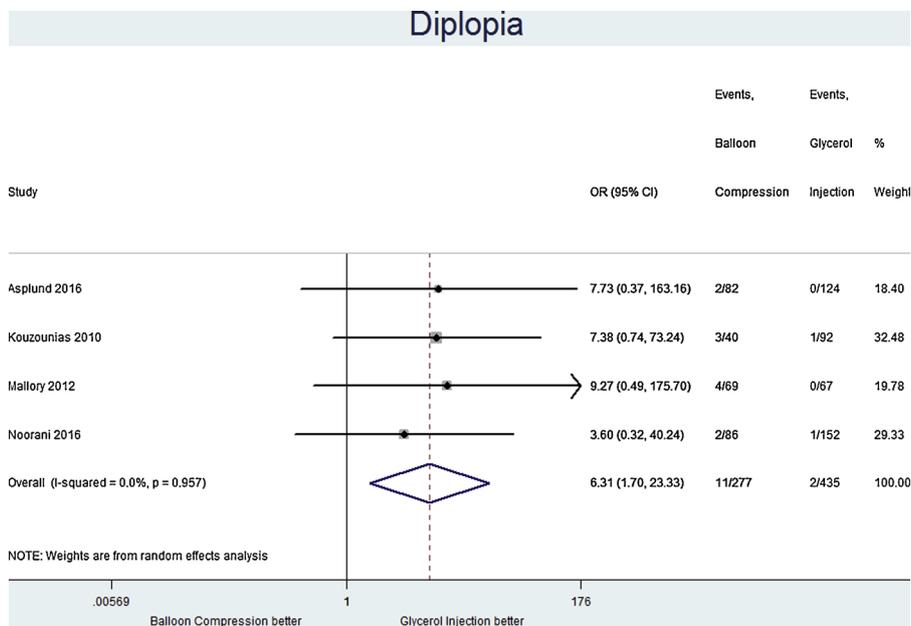


Fig. 9. Forest plot comparing balloon compression vs. glycerol rhizotomy in terms of post-operative diplopia.

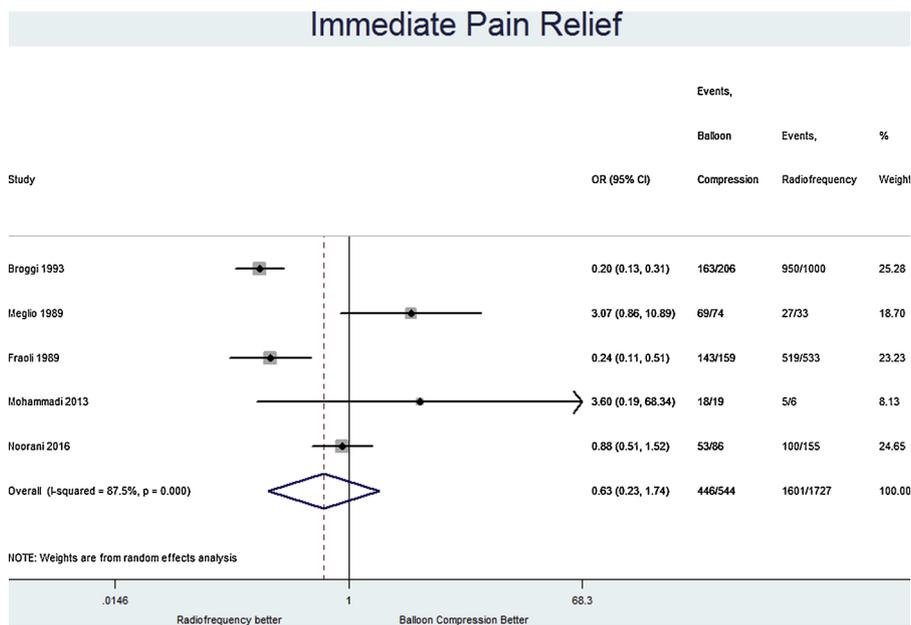


Fig. 10. Forest plot comparing balloon compression vs. radiofrequency thermocoagulation in terms of immediate pain relief.

between the two groups. Asplund et al. suggested that diplopia following BC, is most commonly due to mechanical compression of the cranial nerve IV. [12] Similarly to masseter muscle weakness, diplopia is usually transient and resolves spontaneously. [11,12] In addition, Bergenheim et al. reported that close attention to the position and shape of the inflated balloon should help avoid most diplopia cases [32].

5. Limitations

To date, no randomized trials exist that compare the three percutaneous approaches and it should be stated that performing such studies can be challenging due to the variability of patient populations.

Therefore, current knowledge is based on retrospective comparative studies only. These studies however, are limited by their non-randomized nature and non-blinded design. Over the years, some of the procedural details have been modified. Specifically, the time of compression during BC, or the temperature during RF has shown some variability among the included studies. Also, due to differences in the long-term follow-up intervals between the included studies, we were unable to perform analyses comparing pain recurrence in pre-determined time points (e.g. 6 months, 12 months etc.). In addition, data regarding the patients with immediate pain relief who were on or off analgesic medication were not reported by the majority of the included studies, which precluded further subgroup analyses. Last, we were able to conduct subgroup analyses for patients with MS only;

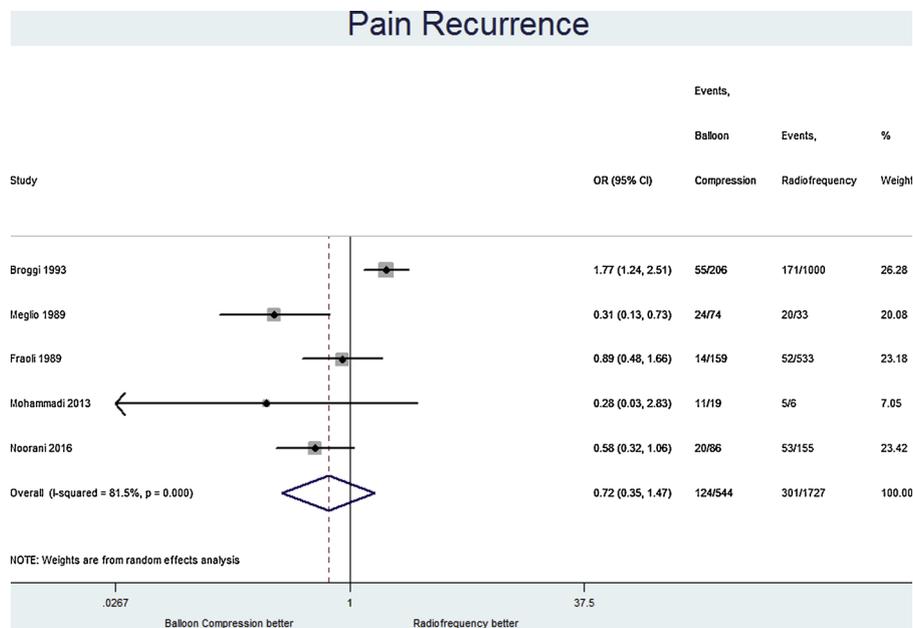


Fig. 11. Forest plot comparing balloon compression vs. radiofrequency thermocoagulation in terms of pain recurrence.

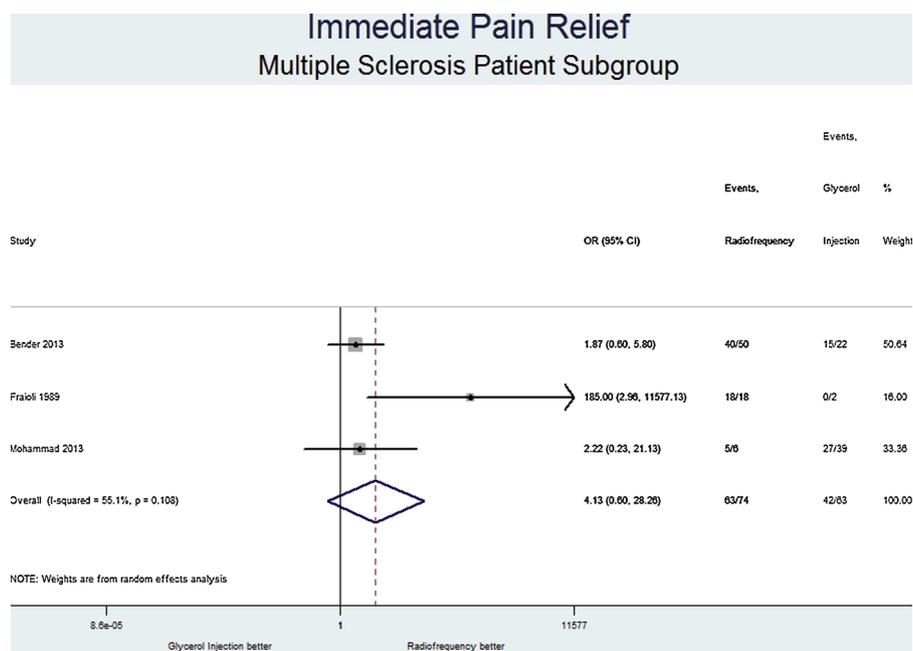


Fig. 12. Forest plot comparing radiofrequency thermocoagulation vs. glycerol rhizotomy in terms of immediate pain relief for multiple sclerosis patients only.

however the etiology of TN was various across the included studies and outcomes were not specifically provided for each different etiology. Future randomized trials are anticipated to validate the results of the present study and provide more insights on the comparative safety and efficacy of the percutaneous approaches for the treatment of TN. For example, a double-blind randomized trial comparing RF vs BC is estimated to be completed on September 2019 (NCT02,427,074).

6. Conclusions

This study suggested that RF provides higher rates of immediate

pain relief when compared to GR; however, this was accompanied by a significantly higher risk for anesthesia in the trigeminal distribution and lower risk for post-operative herpes eruption. Other complication rates were similar between the two groups. Patients who had BC were at a statistically significant higher risk to develop post-operative mastication weakness and diplopia due to cranial nerve IV or VI palsy when compared to GR. No other differences were detected between the BC and GR groups. BC and RF did not demonstrate significant differences in terms of safety and efficacy outcomes. Future RCTs are warranted to validate our results and optimize patient selection.

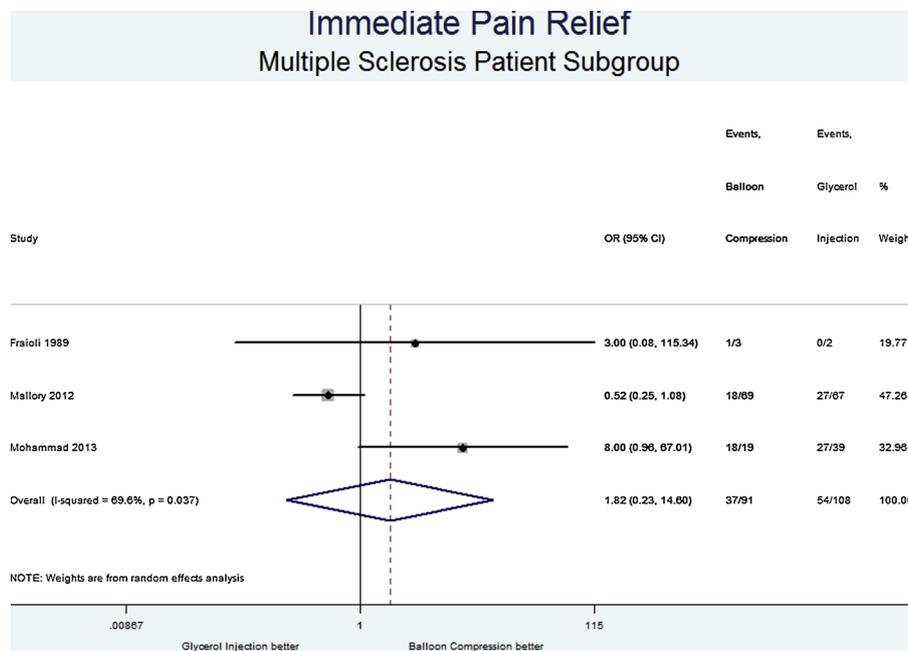


Fig. 13. Forest plot comparing balloon compression vs. glycerol rhizotomy in terms of immediate pain relief for multiple sclerosis patients only.

Disclosure of funding

None.

Conflict of interest

None.

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None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.clineuro.2019.05.011>.

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