Archives of Surgical Research | Meta-analysis

Impact of Branch vs. Truncal Ligation of Inferior Thyroid Arteries on Post-Thyroidectomy Hypocalcaemia: A Meta-Analysis of Controlled Trials

Safia Zahir Ahmad[1], Talat Waseem[2], Zaitoon Zafar[2], Maham Abid[2]

IMPORTANCE Hypoparathyroidism following a thyroidectomy remains a significant clinical challenge for an endocrine surgeon. Recently, it has been proposed by some endocrine surgeons that truncal ligation may lead to a higher incidence of postoperative hypocalcemia, while others have refuted this notion by citing no long-term impact on incidence of hypoparathyroidism.

OBJECTIVE This study aims to compare the effect of truncal versus branch ligation of inferior thyroid arteries on postoperative hypocalcaemia.

DESIGN This is a meta-analysis.

DATA SOURCES Articles were identified using the MeSH, and Free Keyword searches "Thyroid", "Truncal Ligation" and "Hypocalcaemia" in PubMed, Embase, PubMed Central, Cochrane library, Latin American and Caribbean Health Sciences Literature database and Google Scholar.

METHODS Randomized and nonrandomized controlled trials of patients who underwent subtotal/total thyroidectomy, completion thyroidectomy and thyroidectomy with neck dissection were searched, and outcomes of truncal ligation versus branch ligation of inferior thyroid arteries were compared. Quality of methods of randomized controlled trials were reviewed in accordance with Cochrane Collaboration Guidelines on RevMan and non-randomized controlled trials were assessed with Newcastle-Ottawa Quality Scale. Meta-analysis was performed using a random effects model, and pooled results shown as risk differences. The primary outcome was transient postoperative and definite hypocalcaemia.

RESULTS We found 13 randomized controlled trials (RCT) and 11 nonrandomized controlled trials (non-RCT) with 2580 patients: 1267 patients belonged to trunk ligation group and 1261 to the branch ligation group. The risk difference of symptomatic hypocalcaemia was 8% (95% CI :3% to 12%), for biochemical hypocalcaemia; 8% (95%CI: 4% to 13%), and for definite hypocalcaemia was 0% (95% CI: -1% to 1%).

CONCLUSION An increase in the risk of transient postoperative hypocalcaemia is observed following truncal ligation, compared to branch ligation of the inferior thyroid arteries, with no significant risk difference in definite hypoparathyroidism.

KEYWORDS Thyroidectomy, Trunk Ligation, Hypocalcaemia, Inferior thyroid artery, Hypoparathyroidism

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Postoperative hypocalcaemia is a well-established entity following a total thyroidectomy procedure[1]. Most studies have estimated that the incidence of transient hypocalcaemia ranges from 6% to 55%[2,3], while some have even reported up to a 50-68%[4] incidence rate. Moreover, the risk for development of definite hypoparathyroidism has been estimated to be 1-3%[5]. Existing literature states that various patient factors contribute to the development of postoperative hypocalcaemia; such as preoperative calcium and vitamin D levels, the presenting indication for surgery, disease severity and type and size of the gland in addition to surgeon related factors such as surgical techniques, and the respective surgeon's experience[6,7]. However, compromise of the blood vessels to the parathyroid gland or direct trauma to the glands is considered the most important risk factor in the development of postoperative hypocalcaemia[8].

Different surgical strategies and innovations have been brought into practice to prevent the postoperative complication of hypocalcaemia. Some studies have used localization tools to localize the parathyroid gland, and others have used auto-transplantation to prevent postoperative hypocalcaemia[9]. Endocrine Surgeons have revised and refined surgical techniques multiple times in order to avoid inadvertent damage to the vasculature of the parathyroid gland. Such revision of techniques includes utilizing vessel sealing devices, staying in the capsular plane for dissection, and ligating the more delicate branches of inferior thyroid artery near the capsule[10]. As the parathyroid gland is in close relation with the inferior thyroid lobe, and is supplied by the inferior thyroid arteries, experts have proposed that the traditional approach toward ligating the trunk of inferior thyroid artery can lead to hypocalcaemia[11], hence, a more conservative approach towards ligating the branches of inferior thyroid artery has been adopted[8]. However, others like Romano[12] and Dolapci[13] et al. have refuted this notion citing no long-term difference in the incidence of postoperative hypocalcaemia using the branch ligation technique.

Patient related factors
Disease severity
Indication for surgery
Preoperative calcium levels
Preoperative vitamin D levels
Size of gland
Type of gland
Surgery related factors
Surgical technique
Surgeon's experience
Injury to blood vessels

Table 1: Risk factors for the development of postoperative hypocalcemia

The role of ligation of inferior thyroid arteries either at truncal or branch level and its effect on incidence in post-thyroidectomy hypocalcaemia remains a matter of significant scientific debate. Sanabria et al. did a meta-analysis on 9 RCT and 11 non-RCT to demonstrate that the ligation of the inferior thyroid artery increases the risk of temporary hypocalcaemia and that the patient develops symptomatic hypocalcaemia, but the meta-analysis could not establish a risk of definite hypocalcaemia[14]. The meta-analysis had a few methodological compromises; it relied on small individual sample size studies available, and excluded the timing of measuring the outcomes of hypocalcaemia, in addition to excluding cases of malignancy. Recently, a few large sample sized studies have been published which might provide a more credible analysis and compensate for the methodological shortcomings of previous studies.

The objective of this meta-analysis study was to compare the outcomes of truncal ligation of inferior thyroid artery versus branch ligation in postoperative patients of thyroidectomy with additional high quality RCT literature available compared to the last meta-analysis conducted and review the effect of these techniques on postoperative hypocalcaemia.

METHODS

Search strategy and inclusion:

A comprehensive search of controlled trials and analytical studies was conducted on PubMed, PubMed Central, Embase, Cochrane Library and Latin American and Caribbean Health Sciences Literature database and Google Scholars, and studies were time framed from July 1965 to July 2020. The Medical Subject Heading and following term used as Free Text in the search:" Thyroid" OR "Truncal Ligation" AND "Hypocalcaemia". Further expanded data was extracted from articles, and cited authors and references were explored. Language barriers were overcome to include relevant data.

All clinical trials which used the surgical technique of truncal ligation and branch ligation of inferior thyroid artery after bilateral subtotal/thyroidectomy were included. Studies mentioning the use of surgical method of ligation and outcome of hypocalcaemia were selected. Single arm studies/non-comparable studies, reviewers/ letters, abstract articles with no full articles were excluded. Trials and studies of unilateral lobectomies and isthmectomies, capsular dissections without definite artery ligation site, autotransplantations of parathyroid gland following inadvertent removal and studies with undefined methods of inferior thyroid artery point ligation and prophylactic preoperative calcium administration were also excluded.

Population selection and outcome:

Patients undergoing bilateral subtotal thyroidectomy (removal of one lobe and subtotal resection of the contralateral lobe), total thyroidectomy, completion thyroidectomy and thyroidectomy with neck dissection for benign and malignant diseases were the focus of the study. The primary outcome analyzed was postoperative hypocalcaemia. Postoperative transient and definite hypocalcaemia were included according to the author's definition. Hypocalcaemia was divided into biochemical hypocalcaemia with an asymptomatic picture, and symptomatic hypocalcaemia according to serum levels of calcium and ionized calcium. We recorded the serum calcium and parathyroid hormone levels and replacement regimen given.

Data Extraction:

Identified studies were reviewed and the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines were followed15. Two authors screened and identified studies after an extensive search. Any discrepancy in the studies was further reviewed. E-mails were sent to the author and the editor when full-text articles were not available. Duplicated publications were excluded, and a third author confirmed excluded studies.

Further full text articles were reviewed, and eligibility criteria were discussed in case of queries. All data after extraction was counterchecked before analysis. The quality of RCTs was assessed according to the Cochrane collaboration assessment tool16, selection bias was assessed with random sequence generation and allocation concealment, performance bias was assessed by blinding of participant and personnel, detection bias was assessed by blinding outcome assessment, attrition bias and reporting bias. For non-RCTs, nine-point Newcastle-Ottawa assessment scale (NOS) 17criteria was used to assess the quality of the studies. The maximum star awarded for each item was 4 for selection, 3 for the outcome and 2 for comparability. Articles awarded six or more were considered as high-quality studies. The higher the number of scoring, the higher the quality was considered of the study.

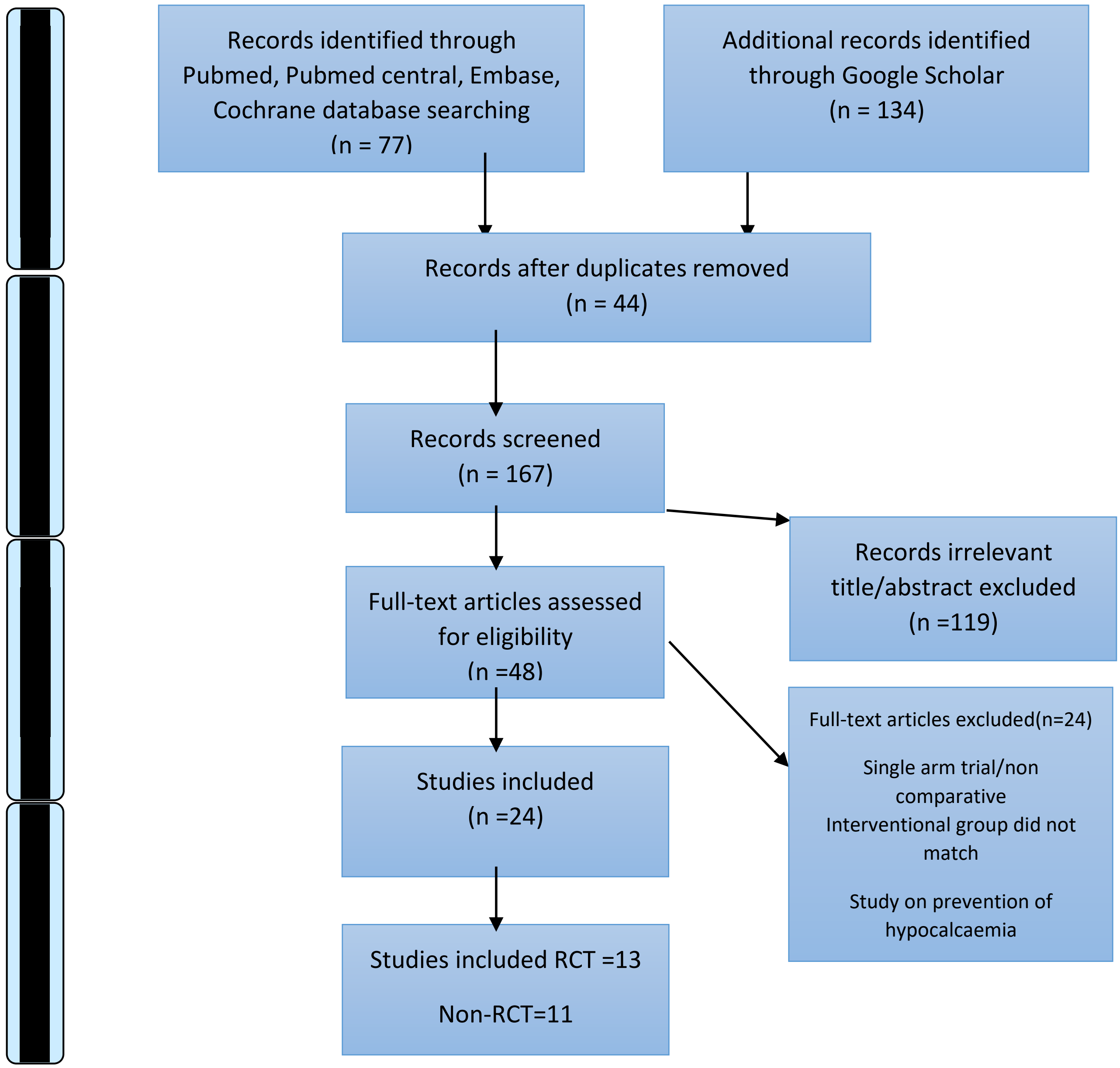

Fig 1. Flow chart showing a selection of studies using PRISMA diagram

Analysis:

The quality of the RCTs and non-RCTs was reported and weaknesses further discussed. A meta-analysis was performed with comparable studies, and variability of population was prevented by using Mantel-Haenszel random effect model. Data for the individual study was obtained for risk difference calculation with chi square test 2x2 table using Review Manager 5.4 software. The meta-analysis is presented as a risk difference (RD) with a confidence interval (95% CI). Results of intervention effects were illustrated with Forrest plot and defined as subgroups of RCT and non-RCT.

Sensitive analysis was conducted by excluding each study in turn, in order to evaluate the influence on the pooled results. Cochran's Q test was used to assess the heterogeneity, I2 test was used for the statistical analysis of the degree of heterogeneity across the studies. The heterogeneity of the individual effect of the studies was assessed with Galbraith and L'Abbe graph, and a funnel plot was constructed for the extent of publication bias. The degree of heterogeneity of interpreting the statistics was as follows: 0-40% may not be significant, 30-60% moderate heterogeneity, 50-90% substantial heterogeneity and 75-100% as considerable heterogeneity.

RESULTS

After an extensive literature search, 211 articles were screened, and 48 studies were assessed for eligibility. 24 studies fulfilling the criteria of the selection process were chosen after a detailed review. Rest of the articles were excluded, as shown in Fig 1.

The study included 13 RCTs[1,5,12,18,-27] and 11 non-RCTs[28 -37] which were reviewed with the characteristics shown in Fig 2. All were prospective studies except for one, which was a retrospective study. Most of the studies included patients who underwent near/subtotal thyroidectomy in bilateral lobes and a total thyroidectomy. 9 studies worked solely on patients undergoing a total thyroidectomy. 1 study included a total thyroidectomy with neck dissection. Malignancy and recurrent thyroid goiter were excluded in all the articles except a recent publication by Waseem et al., which included malignancy and neck dissection and completion thyroidectomy in their trial. All studies monitored serum calcium levels postoperatively, save for 5 studies which did not report their calcium levels. Ionized calcium was monitored in 4 articles. In addition, 10 studies also monitored the parathyroid hormone levels. 7 studies did not mention the symptomatic presentation of hypocalcaemia. Definite hypocalcaemia was not recorded in 9 studies, and 1 study was not clear about which group had definite hypocalcaemia. Serum calcium was mostly monitored on the first postoperative day, except in 4 studies, which monitored on the second day and 2 studies, which monitored on the third day. The follow up time was mostly not recorded in studies except in 3 studies, which followed patients for six months, and another 9 studies, which followed patients for more than six months, and Nies et al. lost 5 hypocalcaemic patients in their follow up period.

Characteristics of studies comparing the Trunk Ligation and Branch Ligation of inferior thyroid artery

	Trunk Ligation Of ITA					Branch Ligation of ITA				
Authors	No. of Pt	Biochemical hypocalcemia	Symptomatic hypocalcemia	Ionised Hypocalcemia	Definite hypocalcemia	No. Of Pt	Biochemical Hypocalcemia	Symptomatic hypocalcemia	Ionised Hypocalcemia	Definite Hypocalcemia
Non-RCT										
Azam 2013	20	7	NR	NR	3	23	5	NR	NR	2
Abou-Amra 2011	20	2	2	NR	0	20	1	1	NR	0
Iqbal 2015	50	12	10	NR	0	50	10	9	NR	0
Chiad 2009	62	50	NR	NR	7	46	22	NR	NR	0
E Ahmed 2011	23	4	NR	NR	NR	27	7	NR	NR	NR
Cakmakli 1992	50	21	7	NR	0	30	13	3	NR	0
Khan 2008	50	11	NR	NR	NR	50	13	NR	NR	NR
Kalliomaki 1961	16	NR	0	NR	NR	17	NR	0	NR	NR
Maralcan 2010	104	15	15	NR	0	126	3	3	NR	0
Salamatullah 2012	30	4	2	NR	NR	30	3	0	NR	NR
Pelizzo 1995	10	3	0	NR	NR	10	5	1	NR	NR
RCT										
Romano 2015	92	51	NR	NR	1	92	39	NR	NR	2
Araujo-Filho 2000	24	5	4	NR	1	24	2	2	NR	0
Naseem 2015	50	NR	14	NR	NR	50	NR	2	NR	NR
Al-Kordy 2019	15	3	3	NR	NR	15	1	1	NR	NR
Cocchiara 2010	63	NR	8	21	2	63	NR	1	10	1
Kebsch 2015	42	12	1	NR	NR	39	22	0	NR	NR
Maralcan 2006	49	NR	1	14	0	49	0	NR	12	0
Nies 1994	50	38	10	15	1	50	37	12	16	1
Sapmaz 2020	68	38	22	NR	?1	71	25	11	NR	?1
Waseem 2020	157	36	36	NR	0	162	5	5	NR	0
Topal 2007	40	NR	4	NR	NR	52	NR	5	NR	NR
Chaudhary 2007	163	10	NR	NR	3	147	7	NR	NR	2
Nawrot 2000	19	8	NR	NR	0	18	7	NR	NR	0

Fig 2. Showing the studies characteristics of randomized control trial and nonrandomized control trial. NR=Not reported

The quality of non-RCTs was assessed using the Newcastle-Ottawa assessment scale and only those studies which scored seven and above, were chosen, as shown in Fig 3. Although there was mention of an adequate follow up of hypocalcaemic patients in the studies, it, unfortunately, could not be applicable for definite hypocalcaemia. RCT studies were evaluated using the Cochrane collaboration assessment scheme, which showed most of the studies were unclear or low risk as shown in Fig 4.

NRCT	Representative	Selection	Ascertainment	Outcome of interest	Comparability	Assessment of Outcome	Length of follow up	Adequacy of follow up	Total
Azam et al 2013	1	1	1	1	2	1	1	1	9
Abou-Amra et al 2011	1	1	1	1	2	1	1	1	9
Iqbal M et al 2015	1	1	1	1	2	1	1	1	9
Chiad et al 2009	1	1	1	1	2	1	1	1	9
E Ahmed et al 2011	1	1	1	1	2	1	1	1	9
Cakmakli et al 1992	1	1	1	1	2	1	1	1	9
Khan et al 2008	1	1	1	1	2	1	1	1	9
Kalliomaki et al 1961	1	0	1	1	2	1	1	1	8
Maralcan et al 2011	1	1	1	1	1	1	1	1	8
Salamatullah et al 2012	1	1	1	1	2	1	0	0	7
Pelizzo et al 1995	1	1	1	1	2	1	1	1	9

Fig 3. Nonrandomized comparative trials quality assessment using New Castle Ottawa Scale Criteria scale.

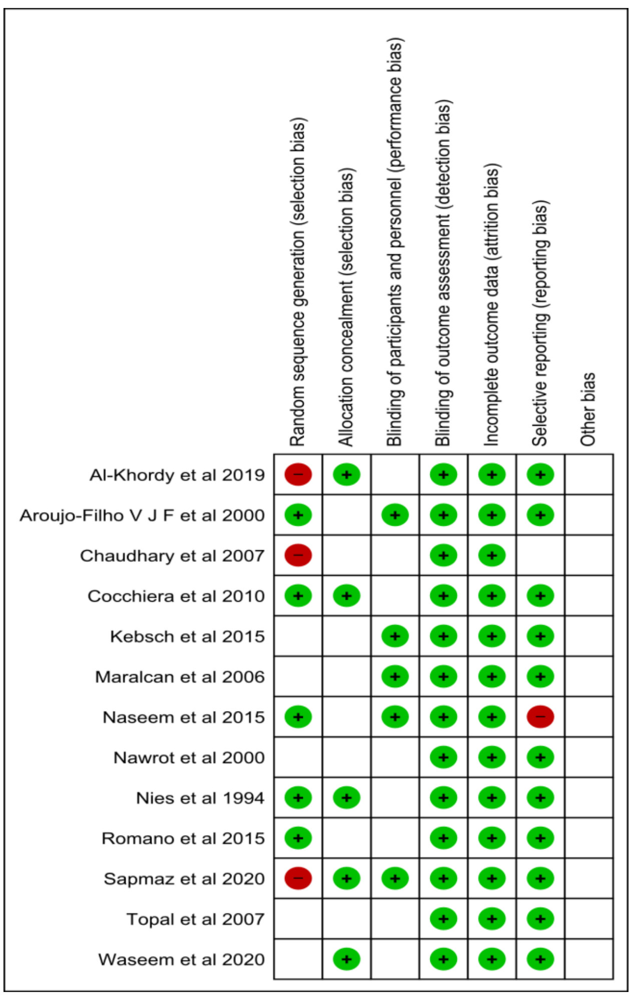

Fig 4. Risk of Bias summary using the Cochrane collaboration assessment tool for randomized control trials. + (Low Risk); - (High Risk); ? (Unclear); A total of 2580 patients were included, 1267 patients who had trunk ligation at inferior thyroid artery group and 1261 patients who had ligation of inferior thyroid artery at branch level.

The number of RCT studies that reviewed postoperative biochemical hypocalcaemia were 11 and 10 were non-RCT. Pooled results of risk difference using Mantel Hansel random effect of biochemical hypocalcaemia was 10% in 1472 patients who were in the RCT group, and 6% in 831 patients in non-RCT group. Out of the 1142 patients in branch ligation group, 235 developed biochemical hypocalcaemia, while 360 patients developed hypocalcaemia out of a total of 1161 patients in truncal ligation group. This indicates a low risk of biochemical hypocalcaemia in branch ligation of inferior thyroid artery with the overall effect of P-value of 0.0005. (Fig 5). Heterogeneity of the study was further explored and by excluding Chiad et al., the heterogeneity decreased to 9% and upon further excluding Chaudhary et al., it resulted in 22% without a change in total RD level.

Symptomatic hypocalcaemia was reported in 10 RCT and 7 non-RCT studies. Risk difference reported in RCT Group was 10% (CI 95% 3-17%) while in non-RCT studies it was 7% (CI 95% 2-11%). In 1133 patients in the RCT group, 48 patients were reported to have symptoms of hypocalcaemia in branch ligation group and 116 were symptomatic in truncal group. In a total of 570 patients in the non-RCT group, 36 were identified to develop symptoms of hypocalcaemia in trunk ligation as compared to 17 patients with a P-value of 0.003. (Fig 6). Pooled results of RD were 8% in total 1703 patients with a higher risk of developing symptomatic hypocalcaemia in ligating the trunk of the inferior thyroid artery.

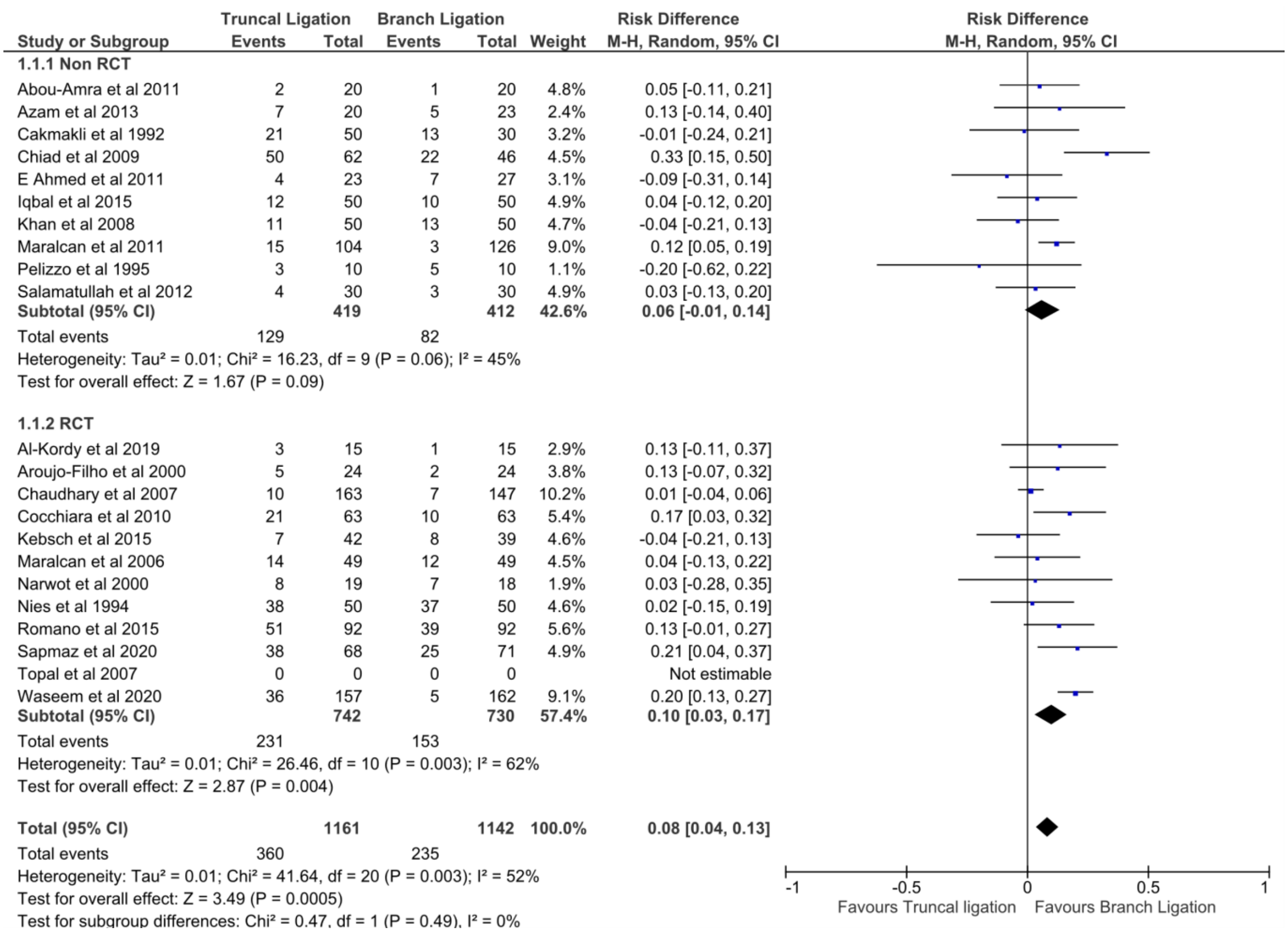

Fig 5. Forest plot for biochemical hypocalcaemia between trunk ligation and branch ligation showing 8% (95% CI 4% to 13%).

Definite hypocalcaemia was documented in 14 studies from both non-RCT and RCT groups, in which total 1962 patients were found. 19 cases developed permanent hypocalcaemia in the truncal group while 8 patients were found in branch ligation group with a pooled RD 0% (CI 95% -1%- +1%). Pooled RD results of non-RCT was 2% in 1703 patients while 0% in RCT group with 1361 patients showing no statistical significance as documented in the literature. Analysis of heterogeneity of the studies was further explored and excluding Chiad et al. reduced the result to 0% (CI 95% 1%-2%) with no global change in pooled results.

Further analysis done between total thyroidectomy and subtotal/total thyroidectomy studies and pooled results of biochemical hypocalcaemia shows 4% (CI 95% 2-9%, I^2=28%) in subtotal thyroidectomy and 15% in total thyroidectomy (CI 95% 11-19%, P-value <0.00001, I^2=0%). In symptomatic hypocalcaemia, 5% (CI 95% 0-9%, P value 0.03, I^2=33%) in subtotal/total thyroidectomy and in total thyroidectomy 13% (CI 95% 7-19%, P value <0.0001, I^2=38%). Analysis of total and subtotal/total thyroidectomy to evaluate the definite hypocalcaemia was 0% with no change in overall pool results.

Asymmetry of publication bias was not found in the funnel plot, as shown in fig 8.

DISCUSSION

Postoperative hypocalcaemia mainly results from an iatrogenic injury of the parathyroid gland during thyroid surgery and decreases the quality of life of the affected total/bilateral subtotal thyroidectomy patient. The incidence of temporary postoperative hypocalcaemia varies, and authors report an incidence range from 6-55% to 83%[8] depending on the age of the patient, size of the gland, type of surgery, the extent of surgery, surgical technique used, the timing of calcium and PTH level checked postoperatively and the outcome. However, definite hypocalcaemia has been reported as 1-2%[24] throughout all published and analyzed literature with no change in its reported incidence rate.

Study or Subgroup	Truncal Ligation Events	Truncal Ligation Total	Branch Ligation Events	Branch Ligation Total	Weight	Risk Difference M-H, Random, 95% CI
2.1.1 Non RCT						
Abou-Amra et al 2011	2	20	1	20	4.5%	0.05 [-0.11, 0.21]
Cakmakli et al 1992	7	50	3	59	6.5%	0.09 [-0.02, 0.20]
Iqbal et al 2015	10	50	9	50	4.8%	0.02 [-0.13, 0.17]
Kalliomaki et al 1961	0	16	0	17	6.6%	0.00 [-0.11, 0.11]
Maralcan et al 2011	15	104	3	104	8.4%	0.12 [0.04, 0.19]
Pelizzo et al 1995	0	10	1	10	2.7%	-0.10 [-0.34, 0.14]
Salamatullah et al 2012	2	30	0	30	6.8%	0.07 [-0.04, 0.17]
Subtotal (95% CI)		**280**		**290**	**40.3%**	**0.07 [0.02, 0.11]**
Total events	36		17			
Heterogeneity: Tau² = 0.00; Chi² = 5.50, df = 6 (P = 0.48); I² = 0%						
Test for overall effect: Z = 2.96 (P = 0.003)						
2.1.2 RCT						
Al-Kordy et al 2019	3	15	1	15	2.7%	0.13 [-0.11, 0.37]
Aroujo-Filho et al 2000	4	24	2	24	3.8%	0.08 [-0.10, 0.27]
Cocchiara et al 2010	21	63	10	63	5.0%	0.17 [0.03, 0.32]
Kebsch et al 2015	1	42	0	39	8.9%	0.02 [-0.04, 0.09]
Maralcan et al 2006	1	49	0	49	9.4%	0.02 [-0.03, 0.08]
Naseem et al 2015	14	50	2	50	5.5%	0.24 [0.10, 0.38]
Nies et al 1994	10	50	12	50	4.5%	-0.04 [-0.20, 0.12]
Sapmaz et al 2020	22	68	11	71	5.3%	0.17 [0.03, 0.31]
Topal et al 2007	4	40	5	52	6.0%	0.00 [-0.12, 0.13]
Waseem et al 2020	36	157	5	162	8.6%	0.20 [0.13, 0.27]
Subtotal (95% CI)		**558**		**575**	**59.7%**	**0.10 [0.03, 0.17]**
Total events	116		48			
Heterogeneity: Tau² = 0.01; Chi² = 38.87, df = 9 (P < 0.0001); I² = 77%						
Test for overall effect: Z = 2.67 (P = 0.008)						
Total (95% CI)		**838**		**865**	**100.0%**	**0.08 [0.03, 0.12]**
Total events	152		65			
Heterogeneity: Tau² = 0.00; Chi² = 42.19, df = 16 (P = 0.0004); I² = 62%						
Test for overall effect: Z = 3.40 (P = 0.0007)						
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.46), I² = 0%						

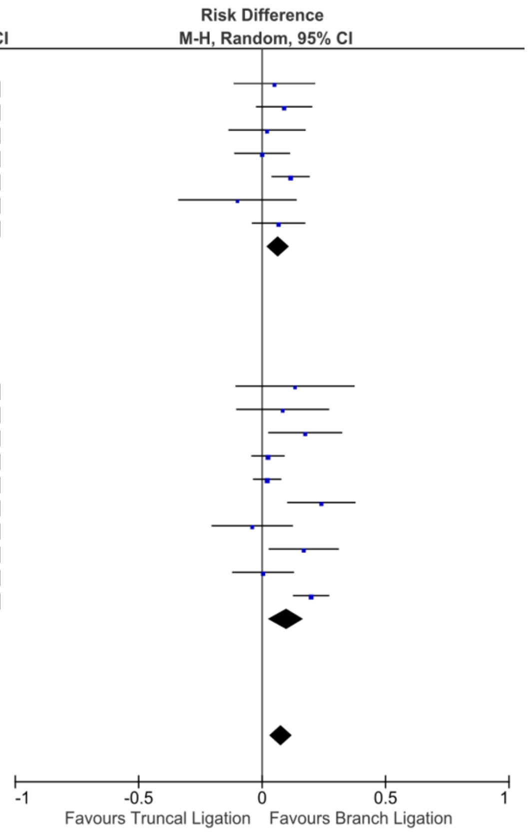

Fig 6. Forest plot in symptomatic hypocalcaemia in Truncal ligation versus branch ligation showing 8% (CI 95% 3-12%) favoring branch ligation group.

Causes of postoperative hypocalcaemia in a previous normocalcaemic patient have been scrutinized at multiple occasions, and literature found that devascularization of the parathyroid gland due to vascular spasm during manipulation or direct injury can result in hypocalcaemia[38]. It was first suggested by Wade et al. in 1965 that infarction of parathyroid gland is due to vascular damage. Postoperative hypocalcemia can result from direct or indirect injury to an artery supplying the parathyroid gland during dissection of thyroid gland. Devascularization has been suggested as an important cause, but vascular spasm and iatrogenic damage to parathyroid gland also causes hypocalcemia. Biochemical hypocalcemia can be explained by manipulation of the gland, with a clear tendency to recover in long term due to redundant vascularization of gland. Different endocrine surgeons in the last decade have tried to find a solution to prevent or minimize this well-known complication by using different techniques.

To overcome this obstacle, it has been suggested to ligate the inferior thyroid artery close to the capsule of the thyroid gland, therefore sparing the main trunk and the preserving the vessel supplying to the parathyroid gland[39]. However, multiple authors cited in this study did not find any major discrepancy of outcome using differing surgical techniques, and their patients recovered similarly to comparative groups of patients who had their inferior thyroid artery ligated near the origin of the vessel[40].

Literature which compares surgical techniques in order to deduce each technique's effect on postoperative, symptomatic biochemical and definitive hypocalcaemia and subsequent use of long-term calcium and replacement regimen, is sparse. Antakia et al[41]. did a systematic review and a meta-analysis to evaluate the role of prevention and other surgical techniques on hypocalcaemia. One of the outcomes reviewed was ligation of trunk of the inferior thyroid artery and they found no impact on temporary or permanent hypocalcaemia. However, the study population reviewed included just 3 RCTs and a single cohort study. The quality of the included studies was also questionable.

In 2017, an up-to standard meta-analysis was conducted by Sanabria et al.[14], focusing on the role of ligation of inferior thyroid arteries on hypocalcaemia after thyroidectomy. The authors found that ligating the trunk of inferior thyroid artery increased chances of the development transient hypocalcaemia, but had no long-term impact on definite hypocalcaemia. Their study, however, was based mostly on low powered studies. Moreover, all selected studies excluded patients who had malignancy, which may confound the outcomes of transient or permanent hypocalcaemia.

Study or Subgroup	Truncal Ligation Events	Truncal Ligation Total	Branch Ligation Events	Branch Ligation Total	Weight	Risk Difference M-H, Random, 95% CI
3.1.1 Non- RCT						
Abou-Amra et al 2011	0	20	0	20	0.7%	0.00 [-0.09, 0.09]
Azam et al 2013	3	20	2	23	0.2%	0.06 [-0.13, 0.26]
Cakmakli et al 1992	0	50	0	30	2.4%	0.00 [-0.05, 0.05]
Chiad et al 2009	7	62	0	46	0.9%	0.11 [0.03, 0.20]
Iqbal et al 2015	0	50	0	50	4.4%	0.00 [-0.04, 0.04]
Maralcan et al 2011	0	104	0	126	21.8%	0.00 [-0.02, 0.02]
Subtotal (95% CI)		**306**		**295**	**30.3%**	**0.02 [-0.02, 0.05]**
Total events	10		2			
Heterogeneity: Tau² = 0.00; Chi² = 15.07, df = 5 (P = 0.01); I² = 67%						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.1.2 RCT						
Aroujo-Filho et al 2000	1	24	0	24	0.5%	0.04 [-0.07, 0.15]
Chaudhary et al 2007	3	163	2	147	8.2%	0.00 [-0.02, 0.03]
Cocchiara et al 2010	2	63	1	63	2.3%	0.02 [-0.04, 0.07]
Maralcan et al 2006	0	49	0	49	4.2%	0.00 [-0.04, 0.04]
Narwot et al 2000	0	19	0	18	0.6%	0.00 [-0.10, 0.10]
Nies et al 1994	1	50	1	50	2.1%	0.00 [-0.05, 0.05]
Romano et al 2015	1	92	2	92	4.8%	-0.01 [-0.05, 0.03]
Sapmaz et al 2020	1	68	0	71	4.1%	0.01 [-0.02, 0.05]
Waseem et al 2020	0	157	0	162	42.8%	0.00 [-0.01, 0.01]
Subtotal (95% CI)		**685**		**676**	**69.7%**	**0.00 [-0.01, 0.01]**
Total events	9		6			
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 8 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Total (95% CI)		**991**		**971**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	19		8			
Heterogeneity: Tau² = 0.00; Chi² = 12.79, df = 14 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.60)						
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%						

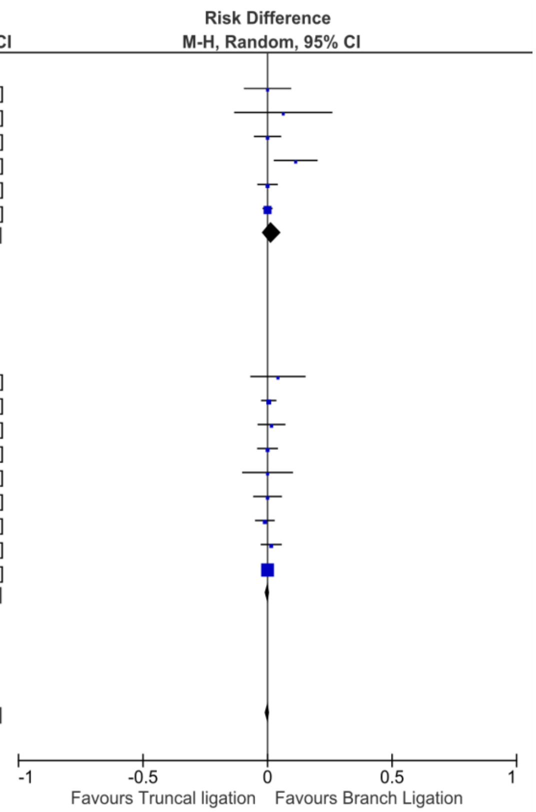

Fig 7. Definite Hypocalcaemia in Truncal ligation compared to Branch ligation with pooled RD of 0%.

One of the authors of this meta-analysis conducted a study on 319 patients and included patients with malignancy and undergoing neck dissection in addition to total thyroidectomy to review the impact of truncal ligation of inferior thyroid arteries on hypocalcaemia[27]. With this largest sample size and robust inclusion criteria, we concur the findings of Sanabria et al. Here we have conducted a new meta-analysis including this large sample sized study using the Cochrane Collaboration Assessment Scheme and PRISMA guidelines.

The quality of the studies was explored in 13 RCTs using Cochrane collaboration assessment tool and found mostly 4 points of low risk of bias with unclear bias and in 11 Cohort studies using the Newcastle-Ottawa scale criteria found to have seven or above stars indicating the good quality studies or acceptable risk of bias making it a reliable to the overall results. Though the quality of these studies was taken into consideration in terms of biochemical and symptomatic hypocalcaemia, but the adequacy of follow up and long-term follow up for definite hypocalcaemia was defined by individual studies varies. Most of the studies followed-up their patients to the extent of the patient remaining asymptomatic or recovering from transient hypocalcaemia.

We used risk difference to estimate the pooled results and random effect due to the large variation of population and heterogeneity to conclude a good reliable outcome result.

Our analysis shows a lower incidence of temporary hypocalcaemia in patients who had branch ligation of inferior thyroid artery with a statistical significance of 8% in biochemical hypocalcaemia with a p value of 0.003 and 8% in symptomatic hypocalcaemia with a P value of 0.0004. For biochemical hypocalcaemia, heterogeneity of the studies decreased to 9% after excluding Chiad et al. and 22% when excluding Chaudhary et al., but the pooled result was consistent with no marked change. Although there was no change in the heterogeneity in symptomatic hypocalcaemia when individual studies were reviewed and excluded. In definite hypocalcaemia, there was no significant difference in the incidence rate in both of the groups with 0% result in agreement with the literature.

Traditionally, it is thought that postoperative hypocalcaemia is multifactorial and is caused by a disturbance in functional levels and removal or manipulation of parathyroid gland which can result in vasospasm[42] or ischemia secondary to ligation of inferior thyroid arteries. Many authors suggest that ligating the main trunk of inferior thyroid arteries is beneficial in terms of preventing on table bleeding and cite no impact on the long-term hypoparathyroidism, hence, they conclude that the benefits of ligating trunk of inferior thyroid arteries outweighs the risk of hypoparathyroidism[21]. In contrast to this notion, this meta-analysis favors ligating the inferior thyroid arteries at their branch level to prevent injury to the main supply of parathyroid gland, which originates 80% of the time from the ITA[38]. Furthermore, studies have shown that during surgical manipulation, the blood flow to the parathyroid gland is compromised, and derangement is seen in serum calcium and serum PTH, with the patient being asymptomatic[12]. This explains the reason for biochemical hypocalcaemia and patient recovery in the postoperative period with no long-term morbidity and dependency of calcium supplements[43,14]. Moreover, patients with malignancy who undergo neck dissection have results similar to patients of non-toxic goitre in terms of temporary hypocalcaemia[44,27].

Limitations

There were a few limitations we encountered during our research; a major limitation was the timing of the serum and ionized calcium levels checked postoperatively. Even though the pooled result did not show any difference, the authors believe it could prove a bias in the results. Similarly, the definition of permanent hypocalcaemia varied in each study and follow up period with calcium replacement regimen was not clearly defined in individual studies to recognize the effects of hypocalcaemia. Moreover, it is not clear whether asymptomatic hypocalcaemia was treated with replacement regimen or not and needs further scrutiny. The extent of surgery performed in bilateral subtotal or a near total thyroidectomy is another factor that can be a cause of heterogeneity with no clear surgical definition. Surgeon's experience and technique on preserving the thyroid tissue can also influence the overall outcome.

CONCLUSION:

In conclusion, branch ligation of inferior thyroid arteries close to its capsule can result in a decrease in the outcome of transient hypocalcaemia and early recovery of biochemical and symptomatic hypocalcaemia but not the risk of the long-term effect on permanent hypocalcaemia. Furthermore, role of truncal ligation of inferior thyroid arteries and its impact on definite hypocalcaemia in long-term follow up requires further research.

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