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Natural History of Conservatively Managed Ureteric Stones: analysis of 6600 patients

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Introduction

Urolithiasis and its management has become a global growing concern posing both clinical and economic burden for healthcare systems (1). With the steady rise of populations, the annual prevalence of urinary tract stones is increasing and as well as the requirement for hospital visits (2).

Ureter stone has a lifetime prevalence of 10% to 15% and is one of the most common urological presentations in the emergency department (3, 4). Patients experience severe flank pain radiating to groin because of sudden obstruction of the ureter, with associated risks of hydronephrosis, renal damage, infection of the urinary tract and severe sepsis (5).

Ureteric stones can be managed by different modalities; expectant management with spontaneous passage of the stone, with or without medical expulsive therapy as an adjuvant (6). Those that fail to pass stones spontaneously will require more invasive options.

In the absence of infection, severe obstruction, renal impairment and uncontrollable pain expectant management of spontaneous stone passage is preferred, as long as the passage is likely in a reasonable time frame (7, 8). There is no clear consensus of recommendations for expectant management of ureteric stones either by the American urological association (AUA) or by the European association of urology (EAU), mainly due to studies with insufficient supporting data. However, current AUA guideline recommends trial of spontaneous passage for ≤ 10 mm stone (9) and EAU recommends the same management for 'small' ureteral stones referring to ≤ 6mm stones, if active removal is not indicated (10).

It is very important to understand the natural history of ureter stone disease especially to recognize the cohort of patients and their stone characteristics, who would expel the stone spontaneously and also to understand the time frame they can be safely observed with least undesirable complications.

However, current literature lacks high-level evidence on spontaneous passage rates. Therefore, we aimed to conduct a systematic review of all randomised trials to better establish an evidence based natural history of stone expulsion, which can aid management

of ureteral stones. In addition, we will look at all studies that specifically researched the natural history of stone expulsion.

Methodology

Search strategy

The systematic review of the literature was performed using Cochrane and PRISMA guidelines (11, 12). The search strategy included the following databases: The US National Library of Medicine's life science database (MEDLINE) (1980- August 2017), EMBASE (1980-August 2017), Cochrane Central Register of Controlled Trials - CENTRAL (in The Cochrane Library - 2017), CINAHL (1980- August 2017), Clinicaltrials.gov, Google Scholar and Individual urological journals.

Search terms used in conjunction with each other included: 'urolithiasis', 'urinary calculi', 'renal calculi', 'ureteric calculi', 'urinary stones', and 'Randomized controlled trial'.

Medical Subject Headings (MeSH) phrases included:

- (("Calculi"[Mesh] OR "Urinary Calculi"[Mesh] OR "Kidney Calculi"[Mesh]) AND "Randomized Controlled Trial" [Publication Type])
- (("Adrenergic Alpha-Antagonists"[Mesh]) AND "Urinary Calculi"[Mesh]) AND "Randomized Controlled Trial" [Publication Type]))
- (("Calcium Channel Blockers"[Mesh]) AND "Urinary Calculi"[Mesh]) AND "Randomized Controlled Trial" [Publication Type]))

Study Selection

All languages were included if data was extractable, also references of searched papers were evaluated for further studies for potential inclusion. Authors were contacted wherever the data was not available or not clear, to be able to adequately assess inclusion of their study. If data was not extractable, provided or clarified, the study was excluded.

Four reviewers (SY, TA, and OA) identified studies that appeared to fit the inclusion criteria for full review. Four reviewers (SY, TA, BS, and OA) independently selected studies for inclusion. Disagreement between the authors in study inclusion was resolved by consensus.

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Data Extraction

Data of each included study was independently extracted initially by 3 authors (SY, TA, and PJ) after which a senior author (OA) extracted the data independently and cross checked each data extraction to ensure quality assurance of data across the board.

All studies comparing a treatment modality to a placebo were included. Published trials on adult patients of placebo arms of stone expulsions and all studies looking at the natural history of stone expulsions were included. We excluded studies on children or stone management studies that did not include a non-treatment arm, ie trials of ESWL, URs, or PCNLs in isolation, with no placebo non-treatment group. We extracted data of the placebo arms of trials, where no medical expulsive therapy or surgical treatment has been carried out, to be able to determine the natural course of stone expulsion and cumulatively analysed these with that of studies reporting the natural history.

The following variables were extracted from each study: patient and stone demographics, expulsion rates, expulsion times, and side effect of the medication. The data of each study was grouped into a meta-analysis, in an intention to treat basis.

Statistical Analysis and Quality Assessment

The data of the placebo arms of each trial was extracted to represent the natural history of stones. We divided each subcategory into overall expulsion rate, stones in the upper, mid, or lower ureter, and stones <5mm and >5mm in size. The results were depicted as percentages and an intention to treat basis was used.

We included all studies looking at the natural history of stone expulsion rates as well as RCTs as these studies are more controlled and more reliable that no intervention was done for the placebo arm and the results are more likely to represent the true natural history of stone expulsion. An assessment of the methodological quality of the RCT was conducted in line with the Cochrane handbook (12).

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Results

Literature search

The literature search identified 876 studies, of which 697 were excluded due to non-relevance based on titles and 179 excluded due to non-relevance based on the abstracts (Figure 1). Full manuscripts were evaluated in 91 studies, of which 22 studies were excluded due to not meeting inclusion criteria. The remaining 70 studies were included that reported on the spontaneous passage of ureteral stones without any medical or surgical intervention (Figure 1) (8,13-81).

Characteristics of the included studies:

The trials span over 3 decades from1994 with the latest in 2017. While the natural history papers spanned from 1977-2017. We were unable to obtain full manuscripts prior to this date to analyse, therefore excluded. There was a total of 6642 patients conservatively treated. The age range was between 17 and 74 years of age. All the natural history studies looked at stone expulsion with no intervention. Table 1 depicts the patient and stone demographics.

All the RCTs reported on the spontaneous stone passage rates with no intervention. Regarding stone location within the ureter, 15 studies reported on upper tract stones, 10 on mid ureteric stones, and 65 on distal ureter stones. Nine studies reporting on more than one location (24, 38, 40, 42, 44, 47, 55, 65, 69). Sixteen studies reported on stones <5mm (29, 33, 34, 39, 40, 44, 46, 48, 55, 69, 75, 76, 77, 79, 80, 81), while 19 reported on stones >5mm.(22, 24, 29, 30,33, 35, 39, 40, 44, 48, 55, 57, 60, 69, 75, 76, 77, 79, 81). Twelve of the studies reported on stones in the distal ureter and >5mm in size (22, 24, 29, 30, 35, 48, 57, 60, 75, 76, 77, 81), while other no studies were found that data can be extracted for stones combining locality and stone size.

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Cumulative analysis results

Stone Passage:

Overall 64.4% patients successfully passed their stones without any medical or surgical interventions (table 2).

Dividing the stones in locality: 49.1% of upper ureteric stones, 58.1% of mid ureteric stones, and 68.1% of distal ureteric stones passed spontaneously (table 2).

Groups based on size: 75.3% of stones <5mm passed spontaneously irrespective of location as opposed to 61.6% of stones >5mm that passed spontaneously (table 2).

Requiring Rehospitalisation:

Nearly 5% required rehospitalisation due to worsening of their condition, ie pain not controlled by analgesics or developed a sepsis (162/3035).

Side Effects:

Only 1% of patients experienced side effects from analgesia provided (31/2745). These included nausea and vomiting being the most common, other side effects included: headaches, dizziness, rhinitis, fatigue, hypotension, diarrhoea, and heartburn.

Methodological quality assessment

All the studies were reported as Randomised controlled studies, ergo considered high quality studies. Figure 2 depicts the summary of the quality assessment based on the reviewing author's judgement of risks of bias for each included study. Of the 63 trials only 12 had no risk of bias to note (17, 30, 32, 33, 37, 54, 55, 62, 65, 66, 67, 81).

One trial did not have appropriate randomisation (50). We found that the blinding was the main differential aspect of the quality assessment between the studies. Only 14 had adequate blinding (13, 17, 22, 23, 30, 33, 37, 53, 55, 62, 65, 66, 67, 81). Furthermore, concealment was not mentioned in many of the trials with 50 not mentioning how they concealed their study giving leaving an unclear decision on concealment, 2 trials made no attempts at concealment (49, 71), while 11 trials had adequate concealment (17, 30, 32,

33, 37, 54, 45, 62, 65, 66, 81). Three studies had incomplete outcomes reporting bias (47, 49, 50). Two other studies had other risk of bias (19, 60).

Regarding the natural history studies, these were of low evidence as they were all cohort retrospective or prospective studies, however each study meticulously delineated their methodology protocol and did not have any evidence of selection or reporting bias, and no missing data.

Discussion

Although it is demonstrated in various studies that small ureteric stones pass spontaneously (8), the urologist are frequently challenged with the decision of whether to observe a stone in expectation of spontaneous passage, or to intervene surgically (82). Studies have also demonstrated that spontaneous passage of ureteric stone is size and location dependent (66, 71). The more the distal the stone is in the ureter, the greater is the probability of spontaneous passage. Additionally, smaller stones are prone to pass quickly when compared to larger stones (8).

We investigated the outcome of ureter stones in 6642 patients treated by expectant management. The incidence of spontaneous passage relating both stone size and location was determined from these collated studies. The rate of spontaneous passage for stones smaller than 5 mm was 75% compared to 62% for those larger than 5 mm, irrespective of their position in the ureter at the time of presentation. While stones discovered in the distal third of the ureter had a spontaneous passage rate of 68%, compared with the mid third of 58%, and the proximal third of 49%. With a low complication rate.

Stones Expulsion Rates

Consideration of various factors is essential to determine the optimal treatment for patients with ureteric stone. Canadian urological association guidelines divides these factors broadly into four categories namely; (i) stone factors consisting of location, size, composition, presence and duration of obstruction, (ii) clinical factors consisting of symptom severity, patient's expectations, associated infection, obesity, coagulopathy, hypertension and solitary kidney, (iii) anatomic factors like horseshoe kidney,

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ureteropelvic junction obstruction and renal ectopia and (iv) technical factors of availability of equipment, expertise and cost. The guideline also emphasizes the selection of any modality of treatment to be based on 'achieving maximal stone clearance with minimal morbidity to the patient (7).

Various studies have demonstrated spontaneous stone passage rate in relation to the stone size; Ueno et al in 1977 showed spontaneous passage rates of 38% and 1.2% in stones of <4 mm and >6 mm (71), Hubner et al in 1993 reported a communitive analysis of the literature, which showed 57% spontaneous passage of stones <4mm, 4 to 6 mm stones passed in 35%, and only 8% in those with stones larger than 6mm (66). Coll et al demonstrated close relationship of stone size and spontaneous passage. They reported stone size of 1, 4, 7 and 10 mm had spontaneous passage rate of 87%, 72%, 47%, and 27%, respectively (65).

The locations of stones also have been well recognized as an important factor in the spontaneous expulsion rate. In 1991, Morse et al demonstrated spontaneous stone passage rate of 71% from the distal 46% from the mid and 22% from the proximal ureter (68). Hubner et al showed spontaneous passage in 38% of stones located in the distal third of the ureter, compared with 15% in the mid third and 18% of stones in the proximal third (66). In a retrospective radiologically followed study using unenhanced CT scan, Coll et al, 2002, reported spontaneous stone passage rate of 75% in distal ureter, 60% for mid ureteral stones and 48% for stones in the proximal ureter (65). Sfoungaristos et al, 2012, noted spontaneous passage of 50% distal ureter stones, including stones in VUJ and 90% passage rate for mid ureter stones (69).

All these studies highlighted how there are discrepancies in the percentages of stone expulsion across the board.

Timing of stone passage

Though these natural history of stone studies, gave a rough idea of the rates of spontaneous stone passage, evidence from RCTs, has shown heterogenic results. The cumulative analysis in this review has yielded a more precise account spontaneous stone passages. However, there remains a great disparity in the time to stone passage between

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all studies, with a wide range from 1 to 4 weeks. Canadian urology guidelines (CUA) and European association of urology recommend 90% of chance of spontaneous passage of stones less than 5 within 40 days (7,10). This review has found that the majority of stone expulsions were within 4 weeks, with an average of about 17 days.

Nonetheless, this was limited by the fact that all the studies included had limited their follow up period to this range, with no longer follow up periods. This was largely based on patient safety. Ergo it can be deemed safe practice to consider treatment after of a stone if it has not passed after 4 weeks.

Safety

The rate of complications has been shown have a direct relation to the duration of symptoms. Twenty percent of patients have complications if symptoms are more than 4 weeks when compared to 7% if symptoms are less than 4 weeks in duration (66). The current study revealed that only 5% required readmission and out of which only 1.1% had minor side effects in relation to the analgesia used.

Implications for practice

Reasonably easy accessibility of equipment (shock wave lithotripsy, semirigid and flexible ureteroscopes) increase in number of trained endourologist and patient expectations has not only expanded the indications for intervention for ureteric stone but also has spawned significant increase in ureteroscopic procedure in last 10years (1, 8). Unfortunately, all form of procedures does come with certain risks.

Observation or expectant management of stone, until stone expels, is one of commonest management option for ureteric stone and appears attractive as it avoids invasive procedure however is associated with ambiguity and uncertainty, pain, potential loss of renal function and most importantly for many, loss of work and family commitments (70).

The continuously debated topic of assisting stone expulsion with medical therapy adds an added question. As shown, α-blockers, specifically tamsulosin, can increase stone expulsion rates of stones in the distal ureter and of those of >5mm. Overall can increase stone expulsion rates by at least 14% (6, 83, 84, 85).

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Furthermore, the cost benefit of conservatory managed stones can also sway decision to avoid treatment. In the United States, it's reported that expectant (observation) management of ureteric stones has a $1200 cost advantage for distal ureteral stones and a $400 for proximal ureteral stones (86).

We believe that current study is the largest cohort evaluation of natural history of ureteric stones and redefines the rate of passage of stones in relation to the size and location compared to previous published literature and current international urolithiasis guidelines. This also briefly gives an idea on the complication rate involved during the observation for the ureteric stones.

Conclusion

Expectant management has undeniable role in the treatment of ureteric stone patients. The outcome is largely determined on the stone size and location of the stone. Most ureteral stones <5mm, especially those located in the mid and distal ureter, will pass spontaneously. Hence it is acceptable for the urologist to observe for spontaneous stone passage for a period of time. Appropriate follow up of these patients is obligatory to avoid complications. If spontaneous passage does not occur within 4 weeks period, intervention is recommended. More importantly, this information helps to reduce patients' anxiety and supports them to make an evidence based informed decision about conservative management as opposed to invasive treatment.

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EAU- European Association of Urology

AUA- American Urological Association

ESWL- Extra Corporal Shock Wave Lithotripsy

URs- Ureteroscopy

PCNL- Percutaneous Nephrolithotomy

RCT- Randomized Control Trial

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Table 1: Demographics of Included studies

Author, yr.	Age (mean+-SD unless specified)	Gender (M:F)	Stone size (mean+-SD unless specified)	**Expulsion rate**	**Expulsion time, d**
Abdel-Meguid 2010	Med 36 (19-72)	53:22	Median 6 (4-10)	42/75	<6m 17; 7-10m 20
Agrawal 2009	35.3 (22-58)	24:10	6.35 (4-8)	12/34	24.5
Ahmad 2015		48	5.78 (4–8)	26/48	
Ahmed 2010	38.9±13.3	19:9	5.39±1.81	14/28	13.9±6.99
Aldemir 2011	43.5 ± 16.6 (18–71)	19:10	6.6 ± 1.7 (4–10)	11/29	7
Autorino, 2005	43	21:11	5.7 (3–10)	19/32	7.4±2.2
Alizadeh 2014	19-54	32:14	0.83±4 .81	30/46	4.7±8.03
Al-Ansari 2010	36.13 ± 9.32		6.04+-2.5	28/46	9.87+-5.4
Bajwa 2013	33.87+-9.61	19:11	6.63+-1.45	11/30	20.93+-4.43
Balci 2014	34.5±10.2	18:7	6.3 ± 1.5	9/25	10.3
Borghi, 1994	43 ± 14	25:18	6.8 ± 2.9	24/43	16.4
Cervenakov, 2002	17–74	33:18		32/51	3.4
Chau 2011	48.6 ± 11.8		6.9 ± 1.5	17/34	-
Coll 2002				115/172	

Cooper, 2000		35	3.86	19/35	11.2
Dellabella, 2003	38.1 ± 10.6 (18-58)	18:12	5.8 ±1.3 (4-11)	21/30	4.6
Dellabella, 2005	39.8 ± 12.7	50:20	6.2 ± 1.7 (4-11.8)	45/70	5
De Sio 2006	44.5 ± 11.3	26:20	6.4 ± 1.3	27/46	7.5±1.8
El-Gamal 2012	36.2 ± 6	34:12	7.7 ± 1.63	12/46	
ElSaid 2015	32.1+-9.2	16:10	5.9+-1.9	7/26	Median 19 (8-25)
Erturhan, 2007				26/60	
Ferre 2009	45 ± 12		3.8 ± 1	24/37	Median 3
Furyk 2015	46 (37–55)			127/155	Median 11
Georgescu 2015	45.14+-11.58	26:24	5.1+-2.02	26/50	12.03+-6.22
Gurbuz 2011	40.3 ± 15.9	22:11	7.13 ± 1.11	3/33	10.55+-6.21
Han, 2006	42.7	22:10	4.3+-0.61	17/32	8.3+-3.8
Hermanns 2009	41 (33–54)	36:9	3.8 (3.4-4.3)	40/45	Median 10
Hubner 1993	47 (10-74)	64:36		30/100	
Ibrahim 2013	36.71 ± 11.64	25:7	5.65+-1.25	14/32	
Itoh 2011	56.5 ± 10.1	92	5.67+-2.1	46/92	15.19+-7.14
Itoh 2013	55.8 ± 10.4	56	4.87+-1.98	31/56	13.4+-5.9
Kaneko 2010	45 ± 8.7 (28–61)	34	4.8±2.1	17/34	17±11

Kang 2009	45.19+-12.27	12:9	0.47+-0.08	8/21	
Keshvary, 2006	n/a	24	6.8	11/24	14.2
Kim 2007	45.7+-13.8	24:18	5.2+-2.6	18/42	18.5+-6.9
Kirac 2013	29.3 ± 7.1	23:16	6.98 ± 2.1	19/39	15.3 ± 5.3
Küpeli, 2004	43.74 (21–65)	15	4.9 (3–5)	3/15	
Lee 2014	47.9 ± 11.4	33:21	3.65±1.15	25/54	19.6±8.5
Liatsikos, 2007	46.33 ± 10.74	6:9	3.00 ± 1.46	9/15	8.8±1.09
	43.75 ± 11.16	7:9	7.69 ± 1.35	7/16	12.1±1.35
Lojanapiwat, 2008	46.52 ± 13.63	20:5	6.70 ± 1.66	1/25	23±0
Lv 2014	33.75+-5.24	18:15	7.3+-1.2	20/33	10.65+-2.92
Miller 1999	36.5			62/75	
Mohseni, 2006	39.3 ± 14.2 (18-61)	24:8	6.6± 3.1 (3.5-10)	20/32	5.9±2.7
Morua 2009	36.2 ± 12.2		6.4+-1.8	6/15	13.16+-11.5
Morse 1991	11-88	242:136		228/378	
Ochoa-Gomez 2011	38.2 ± 12.4	21:12	5.2 ± 0.39	23/33	23 ± 6.36
Pedro, 2008	42.03 ± 12.85	27 : 8	4.07 ± 1.13	27/35	8.5±6.99
Pickard 2015	42.8 ± 12.3	294:85	4.5+-1.7	303/379	15.9+-11.3(84)

Porpiglia, 2000	49 (18-70)	24:24	5.5 ± 1.4	17/48	20
Porpiglia, 2004	42.7 ± 16	16:12	5.4 ± 1.49	12/28	12
Porpiglia, 2006	45.2 ± 0.88 (33–50)	12:12	5.5+-0.13	8/24	
Porpiglia, 2009	46 ± 14.6	23:22	6.03+-0.81	22/45	5
Rahim 2012	33.84+-12.13	31:14	6+-0.53	22/45	19.18+-4.66
Resim, 2005	33.50 ± 9.7	23:7	7.80 ± 2.2	22/30	
Sameer 2014	33.06 ± 8.76	23:12	6.37 ± 1.85	7/35	12.29+-9.46
Sayed, 2008	37.1 ± 9.8 (18-58)	35:10	6.4±1.3 (5-10)	23/45	12.5±2.12
Sfoungaristos	42.40 ± 13.75		7.12±3.57	36/68	
Sur 2015	47 ± 15		5.5±1.6	52/117	-
Sun 2009	37.8+-10.2	24/6	5.7+-1.2	8/30	Median (6 (IQR: 5-7))
Tchey 2011	42.6		3.9±1.8	566/656	
Ueno 1977			4.0 ± 1.5	286/520	
Vincendeau 2010	39.0 ± 11.4	52:9	3.2±1.2	43/61	9.6+-9.8
Wang, 2008	50.9 ± 9.6	23:8	6.5 ± 1.4	17/31	10.1±3
Wang 2016	51.51 ± 10.03		6.46±1.31	48/62	6.31+-2.13
Yencilek 2010	33.5 ± 10.1 (22–51)	30:20	6.6±2.7	15/50	11.6+-4.1

Ye 2017	40 ± 12.3	605:1049	5.7 ± 1.8	1300/1654	10.3
Yilmaz, 2005	41.60 ± 12.01	19:9	6.07 ± 1.41	15/28	10.5±2.12
Yuksel 2015	35.23+-11.2	20:15	6.35+-1.57	25/35	12.91+-6.14
Zehri 2010	33.62	25:7	5.49	12/32	12.5+-1.17
Zhou 2011	34.79 ± 9.63	27:16	6.61 ± 0.74	13/43	9.4 ± 2.48

Table 2: Cumulative analysis of results for the included studies

Parameter	Spontaneous Stone Passage Rate/Total patients (%)
Overall	4277/6642 (64.4%)
Location	
- **Upper Ureter**	348/709 (49.1%)
- **Mid Ureter**	111/191 (58.1%)
- **Lower Ureter**	3442/5056 (68.1%)
Size	
- **<5mm**	1353/1797 (75.3%)
- **>5mm**	1109/1800 (61.6%)

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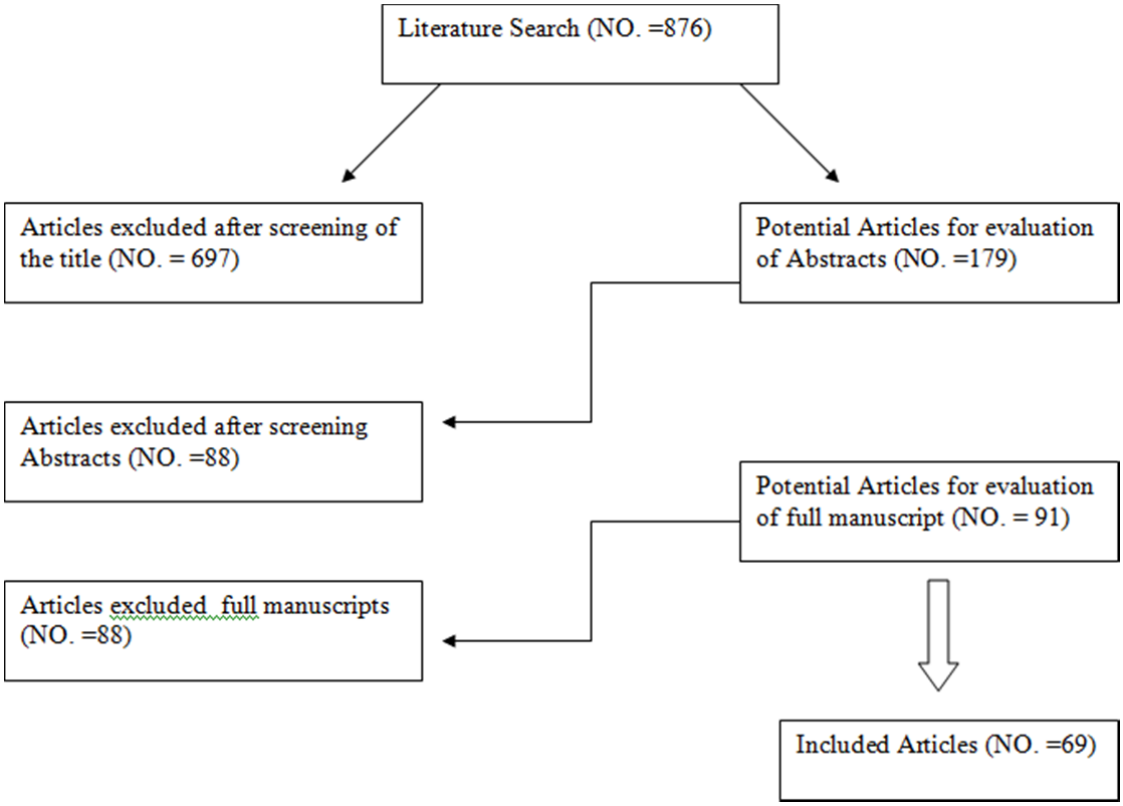

Figure 1: Flowchart for article selection process of the review

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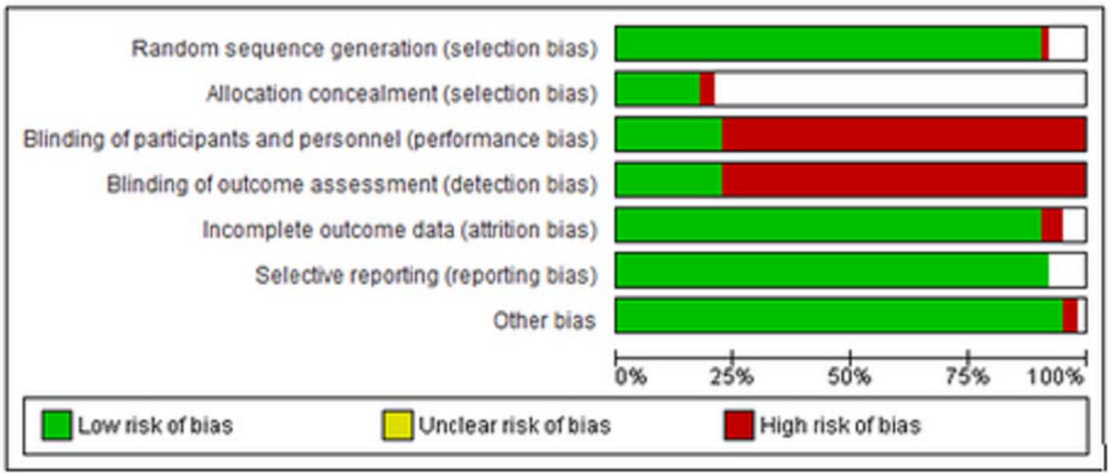

Figure 2 : Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.