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REVIEW ARTICLE

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Are local analgesics effective in reducing autonomic dysreflexia in individuals with spinal cord injury? A systematic review

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STUDY DESIGN: Systematic review.

OBJECTIVES: To systematically review the evidence on the use of local analgesics, specifically lidocaine or bupivacaine, to prevent autonomic dysreflexia (AD) during iatrogenic procedures or bowel and bladder care routines in individuals with spinal cord injury (SCI).

METHODS: A keyword search of MEDLINE, CINAHL, CENTRAL, Cochrane Reviews, PsycInfo, Embase, and Web of Science databases identified all English-language studies evaluating the efficacy of local analgesics in reducing AD. Included studies were either randomized controlled trials (RCTs) or quasi-experimental studies. Participants were adults with chronic SCI who received local analgesics prior to AD-triggering procedures or routines. Additionally, studies were required to report blood pressure values as an outcome. The methodology of this review followed the PRISMA checklist and was registered with PROSPERO (CRD42021219506).

RESULTS: Four RCTs and two quasi-experimental studies met inclusion criteria. Results were narratively synthesized as meta-analysis was not possible due to heterogeneity across studies included in the review. All six studies administered lidocaine. Lidocaine was found to have a beneficial effect on AD in three studies, no effect in two studies and a detrimental effect in one study.

CONCLUSIONS: Presently, RCTs and quasi-experimental studies on the use of lidocaine for reducing AD in individuals with SCI had small sample sizes and opposing findings. There is a strong need for definitive, well-monitored clinical trials with adequate sample sizes. Presently there is not enough compelling evidence to support or refute recommendations for the use of lidocaine from the AD management clinical practice guidelines.

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INTRODUCTION

Autonomic dysreflexia (AD) is a life-threatening hypertensive condition that commonly occurs in individuals with spinal cord injury (SCI), more frequently in those with injuries at the T6 spinal level and above [1]. Although defined as a rise in systolic blood pressure (BP) of ≥20 mmHg triggered by afferent stimuli originating below the level of injury, AD episodes are frequently associated with more pronounced elevation in arterial BP reaching up to 300 mmHg systolic [2, 3] and may result in devastating consequences [4, 5]. Typically, AD is accompanied by severe headache, anxiety, nasal congestion, blurred vision, and bradycardia, as well as flushing, piloerection, and sweating above the level of injury and dry and pale skin below the level of injury. AD is most commonly triggered by events in the lower urinary tract and in the colorectal area [6], and can be iatrogenic in nature, occurring during cystoscopy, urodynamic evaluation, penile vibration, electroejaculation, recto-sigmoid distension and anal manipulation [6, 7]. Untreated episodes of AD have resulted in hemorrhagic stroke, retinal detachment, seizures, and death [8–12]. Therefore, timely recognition and management of AD in individuals with SCI is critical.

The latest version of clinical practice guidelines (published by Paralyzed Veterans of America; PVA) provides numerous pharmacological and non-pharmacological therapeutic modalities for prevention and management of AD [13]. These guidelines outline the steps for identifying and managing episodes of AD and provide an algorithm for treatment. Broadly, most management approaches for AD focus on either preventing or reducing noxious stimuli below the level of spinal cord lesion which trigger AD, accomplished by either removing the noxious stimuli or blocking afferent stimulation via the inactivation of nociceptors. For this reason, common topical analgesics such as lidocaine and bupivacaine are frequently used for bowel management at home and in the clinic. The PVA management guidelines for AD specifically recommend the use of lidocaine jelly for prevention of episodes of AD that could be triggered by urethral or anorectal irritation (e.g., instillation of 2% lidocaine jelly prior to urinary catheterization, rectal examination and stool removal, and the use of lidocaine solution during bladder irrigation) [6]. Local analgesics, such as lidocaine or bupivacaine, block afferent signals by blocking sodium channels [14] and is thus theorized to mitigate

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AD. However, despite topical analgesics being widely used and recommended clinically, the evidence for the impact of lidocaine and bupivacaine on episodes of AD triggered by bowel and bladder management remains inconclusive as several recent studies have reported contradictory findings [15, 16]. Therefore, this systematic review is aimed at assessing the current evidence on the use of topical analgesics to mitigate AD triggered by iatrogenic procedures and daily care routines in individuals with SCI.

METHODS

Methods of search, screening, and analysis were registered on PROSPERO (CRD42021219506). The review was done in accordance with the PRISMA checklist (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [17]. A keyword search was conducted for English-language studies published after 1960 investigating the impact of local analgesics in reducing AD. Searches were conducted in the following databases: MEDLINE, CINAHL, CENTRAL, Cochrane Reviews, PsycInfo, Embase, Web of Science. Population keywords such as *spinal cord injury, tetraplegia, paraplegia*, and *quadriplegia* were paired individually with the intervention keywords *lidocaine and bupivacaine* and with the outcome keywords *blood pressure* and *autonomic dysreflexia*. Full details of the search strategy for the MEDLINE database are demonstrated in Fig. 1. Variations of this search were used, specific for each database. Studies were included if participants were adults (18 + years old) with chronic SCI (>1 year) who received either bupivacaine or lidocaine through any method of administration before or during procedures or routines with potential to trigger AD. For inclusion, studies were required to report BP values. Study designs were limited to randomized control trials (RCTs) and quasi-experimental studies. Manual searches were conducted through references of included articles.

Medline Search (Dates: Jan 1, 1960 – April 21, 2021)
1. (spinal adj3 injur*).ti.ab
2. Tetraplegia.ti.ab
3. Paraplegia.ti.ab
4. Quadraplegia.ti.ab
5. exp Spinal Cord Injuries/
6. exp Paraplegia/
7. exp Quadriplegia/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Lidocaine.ti.ab
10. exp Lidocaine/
11. xylocaine.ti.ab
12. bupivacaine.ti.ab
13. exp Bupivacaine/
14. lignocaine.ti.ab
15. Marcaine.ti.ab
16. Chirocaine.ti.ab
17. levobupivacaine.ti.ab
18. local anesthetic*.ti.ab
19. exp Anesthetics, Local/
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp Autonomic Dysreflexia/
22. (autonomic adj3 dysreflexia).ti.ab
23. (autonomic adj3 hyperreflexia).ti.ab
24. dysreflexia.ti.ab
25. exp Blood Pressure/
26. (blood adj3 pressure).ti.ab
27. 21 or 22 or 23 or 24 or 25 or 26
28. 8 and 20 and 27
29. Limit 28 to English language

'exp' = explode MeSH search terms
'/' = include MeSH search terms
'.ti,ab.' = search title and abstract for keywords,
'' = include keywords with varying endings.*

Fig. 1 Search strategy. An example of the search strategy from MEDLINE database is described.

abstract and full-text review were performed by three independent reviewers, such that each study was rated by at least two reviewers. Conflicts were resolved by discussion leading to a mutual consensus. Twenty non-English studies were translated with Google translate and were excluded during abstract search because they did not meet inclusion criteria. Data extraction tables were designed by three authors in collaboration. Two reviewers independently collected data for each article. Information extracted from each paper included: (1) authors, country where study was conducted, study design and quality assessment results; (2) methodology (including participant population, procedure with potential to trigger AD, analgesic intervention, and outcome measures); and (3) primary outcomes and conclusions from each study (Table 1). See Fig. 1 for the exact search strategy used for the MEDLINE database. To assess quality and risk of bias in individual studies, we used version 2 of the Cochrane Risk of Bias Tool for RCTs [18] and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for quasi-experimental studies [19]. To create a "Low, Moderate, or High" judgment of overall quality for each study, we used the principles outlined by the Cochrane Risk of Bias Tool [18]. The systematic review software Covidence was used for eligibility assessment, full-text review, and quality assessment.

RESULTS

Study selection

The database search produced 243 citations in total (Fig. 2). Once duplicates were removed, 187 citations were screened for eligibility. A review of titles and abstracts resulted in the exclusion of 120 studies as these did not meet the inclusion criteria. The full texts of 67 articles were reviewed in detail; in the end, 61 studies did not meet the inclusion criteria. No unpublished studies were included. No additional studies were identified via the manual search. In the end, 6 studies met the inclusion criteria and were ultimately included in the review [15, 16, 20–23].

Risk of bias

The results of the Cochrane Risk of Bias Tool for RCTs [18] and JBI Critical Appraisal Checklist for the quasi-experimental studies [19] are presented in Table 1. No studies were excluded on the basis of quality level. Of the four RCTs, one study was judged to have low risk of bias [21], another study had moderate risk of bias [20] and the other two studies had high risk of bias [15, 16]. With respect to the two quasi-experimental studies, one study was judged to have low risk of bias [23] and the other had high risk of bias [22].

Study characteristics

A meta-analysis was not appropriate for this systematic review due to limited number of relevant studies, with considerable heterogeneity across the design, procedures/routines, interventions and reported outcome measures. Therefore, the present review is focused on a qualitative narrative synthesis.

Design and participant characteristics. Table 1 summarizes the design and participant characteristics of the 6 studies included in the review. Four studies were RCTs [15, 16, 20, 21] and two studies lacked randomization and thus were of quasi-experimental design [22, 23]. Three studies were conducted in the USA [20, 21, 23], two in Canada [16, 22] and one in Japan [15]. The publication years of the studies spanned greater than 20 years from 1997 to 2020 and included 280 procedures and 165 patients (some procedures were

Table 1. Summary of study characteristics and outcomes.

Authors, year; country study design quality assessment	Methods	Outcomes & Conclusion
Bowel procedures		
Cosman, Vu & Plowman, 2002; USA Prospective double-blind placebo-controlled trial Moderate[a]	Participants: $N = 50$ procedures in 45 patients (44 M, 1 F) with injury levels >T6 and severity AIS A Procedure: anoscopy with or without hemorrhoid ligation and/or flexible sigmoidoscopy Analgesic intervention: Instillation of lidocaine into the anal canal ($n = 18$) or control with no lidocaine ($n = 32$) Outcome measures: SBP	1. There was no significant difference in mean maximal SBP elevation from baseline between the lidocaine (35 ± 25 mmHg) and control groups (45 ± 30 mmHg) for all procedures. 2. Maximal SBP increase was higher in patients who underwent anoscopy (49 ± 29 mmHg) compared to flexible sigmoidoscopy only (25 ± 20 mmHg) Conclusion: Instillation of lidocaine into the anal canal did not significantly limit or prevent severity of AD
Cosman & Vu, 2005; USA Randomized placebo-controlled trial Low[a]	Participants: $N = 26$ procedures in 25 patients (24 M, 1 F) with injury levels C3-T4 and severity AIS A Procedure: anosopic hemorrhoid ligation and/or flexible sigmoidoscopy Analgesic intervention: injection of lidocaine into anal verge ($n = 13$) or placebo ($n = 13$) Outcome measures: SBP	1. Maximal SBP elevation was significantly lower in lidocaine group (22 ± 14 mmHg) than placebo group (47 ± 31 mmHg) for all procedures. 2. For procedures involving only flexible sigmoidoscopy, maximal SBP elevation was lower in the lidocaine group (21 ± 8 mmHg) compared to placebo (42 ± 27 mmHg). 3. For procedures involving anoscopic hemorrhoid ligation, there was no significant difference in maximal SBP increase between lidocaine and placebo group. Conclusion: Injection of lidocaine into the anal verge mitigated AD triggered by anorectal procedures.
Furusawa et al, 2009; Japan Prospective double-blind crossover quasi-experimental study Low[b]	Participants: $N = 25$ patients (22 M, 3 F) with injury levels C4-C7 and severity range AIS A-B Procedure: bowel routine in clinic Analgesic intervention: Instillation of lidocaine into the anal canal and non-lidocaine jelly Outcome measures: SBP, HR, incidence of AD	1. Incidence of AD was lower in the lidocaine condition (four patients) compared to the placebo condition (ten patients). 2. Mean maximal increase in SBP during bowel routine with lidocaine treatment (33.2 ± 14.6 mm Hg) was less than with placebo (50.2 ± 19.5 mm Hg) for all subjects. 3. SBP values during bowel manipulation (at insertion of medication into the rectum, and from first digital rectal stimulation to 5 min after end of stool flow) were significantly lower in the lidocaine treatment condition than placebo. 4. Heart rate did not change throughout the bowel program in either treatment condition nor was there any difference between conditions. Conclusion: Instillation of lidocaine into the anal canal reduced the severity of AD but did not completely prevent it.
Lucci et al, 2020; Canada Randomized placebo-controlled clinical crossover trial High[a]	Participants: $N = 13$ patients (9 M, 4 F) with injury levels C3-T4 and severity range AIS A-C Procedure: bowel routine at home Analgesic intervention: Lidocaine rectal lubricant and standard (placebo) lubricant Outcome measures: SBP, HR, time-to-complete bowel care	1. Incidence of AD was the same in the lidocaine condition and placebo condition (100% incidence in AD in both conditions). 2. Peak SBP during bowel routine was significantly higher in the lidocaine group (214.3 ± 10.5 mmHg) compared to the placebo group (196.7 ± 10.01 mmHg). 3. Maximal increase in SBP during bowel routine was not different between lidocaine condition (90.5 ± 13.4 mmHg) and placebo condition (80 ± 8.6 mmHg). 4. Mean SBP during bowel routine was not different between and lidocaine condition (135.7 ± 6.7 mmHg) and placebo condition (126.7 ± 7.5 mmHg). 5. There were no significant differences between placebo and lidocaine in the incidence of episodes of bradycardia or tachycardia during bowel routine. 6. Time to complete bowel care was significantly longer in the lidocaine condition (79.1 ± 10.0 min) compared to the placebo condition (57.7 ± 6.3 min). Conclusion: Lidocaine was not effective in reducing AD and prolonged bowel care but did not increase incidence of cardiac abnormalities.

Table 1. continued

Authors, year; country study design quality assessment	Methods	Outcomes & Conclusion
Urologic procedures		
Solinsky & Linsenmeyer, 2019; USA Prospective observational cohort study High[b]	Participants: $N = 50$ patients (43 M, 7 F) with injury levels C1-T6 and severity range AIS A-D Procedure: Catheter change Analgesic intervention: intravesical lidocaine instillation, either before catheter removal (treatment group, $n = 27$) or after catheter removal but prior to replacement (control group, $n = 23$) Outcome measures: SBP, incidence of AD	1. Mean SBP increase post catheter change was lower in the treatment group (9.5 mmHg) compared to the control group (26.9 mmHg). 2. 14.8% of individuals in treatment group experienced AD with catheter change vs 47.8% in control group. Conclusion: Pre-treatment with intravesical lidocaine prior to routine catheter change significantly reduced the incidence of AD and magnitude of systolic blood pressure rise during catheter change.
Other procedures		
Matthews et al, 1997; Canada Randomized 2-factor repeated measures, double-blinded trial High[a]	Participants: $N = 7$ patients (6 M, 1 F) with injury levels C4-T1 and severity range AIS A Procedure: FES of quadriceps muscle Analgesic intervention: Lidocaine/prilocaine EMLA cream and placebo cream applied to the stimulation site Outcome measures: SBP, HR, signs & symptoms of AD	1. As stimulation intensity increased, SBP increased, and HR decreased in both lidocaine/prilocaine and placebo cream conditions. 2. There were no differences in SBP or HR between lidocaine/prilocaine and placebo conditions. Conclusions: SBP and HR were unaffected by use of lidocaine/prilocaine cream on skin at FES site.

AD autonomic dysreflexia, *AIS* ASIA Impairment Score, *ASIA* American Spinal Injury Association, *BP* blood pressure, *EMLA* eutectic mixture of local anesthetics, *F* female(s), *FES* functional electrical stimulation, *HR* heart rate, *M* male(s), *NS* not specified, *SBP* systolic blood pressure, *SCI* spinal cord injury.
[a]Methodological quality assessment based on Cochrane RCT quality assessment tool.
[b]Methodological quality assessment based on JBI Quasi-Experimental quality assessment tool.

performed more than once in the same patient). Gender and level/severity of SCI were reported for all studies. Most participants were male, consisting of 89.7% of all participants. All participants had either high thoracic or cervical SCI.

Procedures and interventions. For consistency and clarity, "procedure" refers to any potential AD triggering event that participants underwent. Four studies were related to bowel care routines or procedures [15, 16, 20, 21], one study was related to urological care (e.g., catheterization) [23] and one was related to functional electrical stimulation [22]. Although bupivacaine was included as a search term during the database search, none of the included studies used bupivacaine; only lidocaine or a lidocaine/prilocaine combination were used as the intervention in all studies [15, 16, 20–23]. As such, from this point forward, "intervention" refers to administration of lidocaine. The administration methods included anal block injection [20], rectal insertion of lubricant [15, 16, 21], intravesical instillation of lubricant [23] and topical cream [22].

Outcomes. The primary outcome of most studies was the impact of lidocaine on AD during procedures, reported as SBP changes and/or AD incidence by number of participants (Table 1). All studies either reported peak SBP or change in SBP from baseline. AD symptoms such as headache, sweating or flushing were also reported when present. Additional outcomes reported by some studies included time-to-completion of procedure, heart rate (HR) and cardiac rhythm. No study reported on adverse events or complications due to prolonged AD such as retinal hemorrhage or death.

Effects of lidocaine on AD severity

Overall, three studies reported lower SBP values or AD incidence with use of lidocaine compared to control/placebo [15, 20, 23] and two studies reported no difference in SBP values or AD incidence [21, 22]. One study reported that the use of lidocaine may worsen AD because the absolute maximum SBP was higher in the lidocaine condition compared to the placebo condition [16]. Regarding the secondary outcome, HR changes, two studies reported no differences in HR changes with use of a lidocaine compared to placebo [15, 22]. Only one study investigated cardiac arrhythmias but the relationship between lidocaine interventions and cardiac arrhythmias was unclear [16].

Bowel sub-group synthesis. Intricacies of lidocaine's effect on AD are revealed by examining the four studies related to bowel care in more depth. Two studies compared the use of lidocaine versus placebo lubricant during bowel care routines and had conflicting findings [15, 16]. Furusawa et al. [15] demonstrated lidocaine lubricant was effective in reducing the severity of AD although AD was not completely prevented. In this study, SBP during the bowel routine in the lidocaine condition was still elevated compared to baseline values; however, maximal SBP was significantly lower than in the placebo condition, and SBP returned to baseline values at an earlier point during the routine in the lidocaine condition compared placebo. Additionally, four patients reported AD symptoms in the lidocaine condition compared to ten patients in the placebo condition. There were no HR changes in either condition [15]. On the other hand, Lucci et al. [16] concluded that lidocaine lubricant was not only ineffective at reducing AD but may even worsen AD. Maximal SBP was significantly higher and time to complete the bowel care routine (i.e. time spent at risk of triggering AD) was significantly longer in the lidocaine condition compared to placebo. However, there was no significant difference between conditions for mean SBP during bowel care nor when maximal SBP was compared to baseline, which could be attributed to the lack of stable BP during baseline due to distended bowel [16, 24, 25].

Two other studies compared lidocaine to placebo during a variety of anorectal procedures and found differing results [20, 21]. Cosman, Vu & Plowman found that topical lidocaine did not significantly reduce the SBP elevation from baseline compared to placebo, regardless of the type of anorectal procedures [21]. The same group later found an anal block with lidocaine injections was effective in reducing the maximal SBP increase from baseline compared to placebo during procedures involving flexible

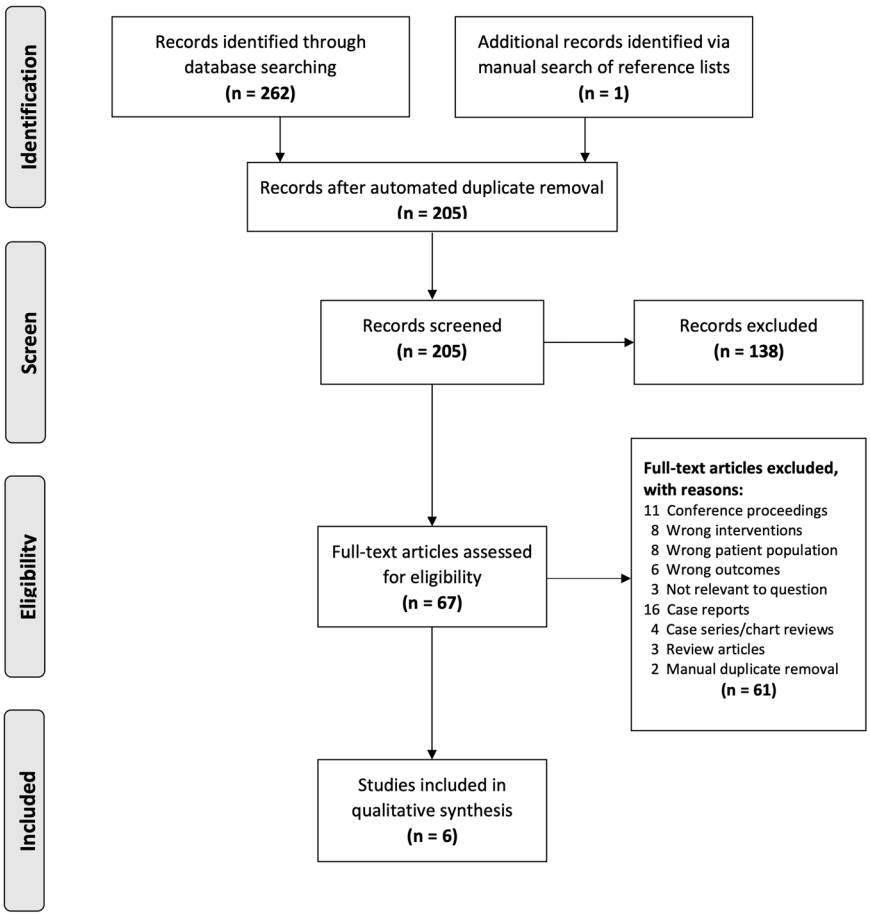

Fig. 2 Study design. A PRISMA style flowchart of study selection shows the key steps of study design from identification to screening, eligibility assessment, and inclusion into the analysis.

sigmoidoscopy [20]. However, lidocaine anal block was ineffective at blocking AD during procedures involving anoscopy, which is theorized to have a stronger sphincter stretch stimuli.

DISCUSSION

The objective of this systematic review was to investigate the evidence on the clinical use of lidocaine for reducing AD in individuals with SCI. Given how commonly AD occurs in the SCI population [26] and the severity of complications that may result from AD [5], having effective strategies for managing AD is of utmost importance [6]. Patients with SCI undergo frequent medical procedures and engage in daily care routines, both of which can be triggers of AD [3, 7, 13]. Identifying effective strategies to prevent AD during medical procedures and routines would significantly reduce the risk of complications.

Of the six studies that were included in our review, lidocaine was found to be beneficial in three studies. However, two studies found no effect of lidocaine on AD triggered by procedures and one study found a detrimental effect. The administration method of the lidocaine and the AD triggering procedures varied widely across the included studies, preventing any patterns from emerging. Additionally, the overall risk of bias in four RCTs and two quasi-experimental studies is inconsistent, making it challenging to compare findings across studies. Finally, no meta-analysis or summary statistics were performed due to significant heterogeneity of studies. Overall, insufficient number of studies and wide diversity of the AD triggering procedures prevented any conclusive recommendation regarding the general use of lidocaine during AD triggering procedures.

Despite the majority of studies focusing on bowel care routines and anorectal procedures, no clear conclusions could be drawn due to opposing findings. With respect to reducing severity of AD during bowel care routines, the results of Furusawa et al. [15] support the use of lidocaine lubricant applied rectally prior to the routine; while Lucci et al. [16] found a detrimental effect of lidocaine lubricant on AD under similar clinical circumstances.

Two studies investigated the use of lidocaine to prevent or reduce the severity of AD during bowel procedures such as anoscopy and/or flexible sigmoidoscopy [20, 21]. These two studies are interesting to compare to one another because they were done by the same research group with one study using topical lidocaine [21] and the other using injectable lidocaine to create an anal block [20]. In the study by Cosman and Vu [20], it is unclear why a lidocaine anal block was effective at reducing AD during flexible sigmoidoscopy but not during anoscopy. We theorize that this could occur because anoscopy is theoretically a stronger stimulus for the anal sphincter than flexible sigmoidoscopy. Additionally, the dense innervation of the anal sphincter could make anoscopy a stronger stimulus when compared to stimulation that involves visceral organs such as the rectum or the colon. Higher concentrations or stronger analgesics may be necessary to counteract stronger stimuli. However, this relationship requires further investigation.

At the present time, clinical practice guidelines by the Consortium for Spinal Cord Medicine recommend the use of 2% lidocaine jelly prior to catheter change and bowel care in individuals with SCI [6]. However, these guidelines rely heavily on clinical consensus. More robust studies are needed to make an accurate decision about whether to support or revise these

guidelines. Overall, from a clinical standpoint, our review found no clear conclusion to offer practitioners caring for patients with SCI regarding the use of lidocaine during AD triggering procedures.

LIMITATIONS

A limitation of note for the current systematic review includes the lack of consistent outcome measures limited comparisons between studies. As a meta-analysis was not performed, no request was made to authors to provide additional data. While obtaining consistent outcome measures across studies may have eased comparisons, given the small number of studies identified by this review, little additional insight would have been gained. Additionally, gray literature was not included in this review; therefore, the possibility exists that this literature could resolve some of the conflicts identified by this review. Finally, since the studies did not consistently report AD symptomology concurrent with the increase in SBP, it is challenging to differentiate between average increase in SBP and symptomatic AD based on the current literature.

CONCLUSION

Presently there is inconclusive evidence regarding whether lidocaine is effective in reducing iatrogenic AD during medical procedures or care routines for patients with SCI. Half of the published literature states that lidocaine is effective at reducing AD whereas the other half states that it is ineffective or detrimental. In sum, there is no compelling evidence to support or refute the use of lidocaine from the AD management clinical practice guidelines. Regardless, there is a strong need for definitive, well-monitored clinical trials with adequate sample sizes to strengthen the evidence regarding the role of lidocaine in AD management.

DATA AVAILABILITY

Additional data may be provided by the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

WS, KG, RS, and AK designed the review. WS and KG conducted the database search. WS, KG, and LM screened and selected eligible articles, extracted the data and analyzed the quality of the included studies. Any discordance was settled by consensus between WS, KG and LM. WS, KG, and LM interpreted the results and wrote the first draft of the report. RS and AK provided theoretical feedback throughout the review process. WS, KG, KK, RS, and AK provided feedback on the manuscript and made edits to the final version. All authors approved the submission of the manuscript and declare no conflicts of interest.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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