Title: Safety and efficacy of intravenous hydralazine and labetalol for the treatment of asymptomatic hypertension in hospitalized patients: a systematic review

ABSTRACT

Background: Current guidelines for the management of asymptomatic hypertension (HTN) in the inpatient setting recommend the use of oral antihypertensives. However, in clinical practice, intravenous (IV) antihypertensives are commonly utilized with little supporting evidence. The objective of this study was to evaluate literature examining the safety/efficacy of IV hydralazine and labetalol in hospitalized patients with non-emergent, asymptomatic HTN.

Methods: The PRISMA guidelines were utilized to structure the systematic review. A search strategy composed of drug-, inpatient-, and HTN-related terms was conducted utilizing PubMed, Embase, and Scopus databases through May 2020. Full-text, English-language articles describing IV labetalol and/or hydralazine use for non-emergent HTN in an inpatient setting that focused on clinical outcomes (i.e. vitals, adverse effects, healthcare utilization) were included. Identified studies were screened/extracted using DistillerSR by two reviewers at each stage, and studies were evaluated qualitatively for the presence of bias.

Results: From 3362 records identified in the search, a final set of 10 articles were identified. Four studies focused on labetalol (40%), five studies on hydralazine and labetalol (50%), and one study on hydralazine (10%). The included studies presented a variety of outcomes, but several trends were identified, including reduction in average blood pressure in eight (80%) studies, a risk of adverse effects in six (60%), and increased length of stay in one (10%).

Discussion: The studies identified in this review raise concerns regarding the safety of IV hydralazine and labetalol in non-emergent HTN. Despite relatively broad clinical experience with these drugs, experimental investigations regarding their utility are recommended.

Keywords: antihypertensives; hypertensive urgency; hydralazine; labetalol

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MAIN TEXT

Introduction

It is estimated that 1 billion people worldwide—including 72 million Americans—are affected by hypertension (HTN), and 1% of all patients with HTN will develop a hypertensive crisis at some point in their lifetime, requiring clear guidance on the management of these acute elevations in blood pressure (BP).[1] Generally, HTN is a disease characterized by chronically elevated systolic and/or diastolic BP, primarily managed in the outpatient setting with oral medications, dietary adjustments, and other lifestyle modifications. However, hypertensive crises may occur in cases of acutely elevated BP (>180/120 mmHg). Hypertensive emergency is a serious form of hypertensive crisis, which includes elevated BP in addition to end organ damage, resulting in complications, such as retinopathy, pulmonary edema, or other manifestations, the presence of which determines whether a patient is experiencing hypertensive urgency (lack of end organ damage) or emergency.[2]

Acute, sustained elevations in BP cause concern for the risk of a patient experiencing hypertensive emergency. However, in the absence of end-organ sequelae, the optimal treatment of HTN urgency is unclear. In the United States, the Joint National Committee (JNC) 7 guidelines recommend oral (PO) antihypertensives as the mainstay of treatment for hypertensive urgency, with a focus on outpatient treatment and close monitoring;[3] recommendations from the 2017 guideline on hypertension from the American College of Cardiology (ACC) and the American Heart Association (AHA) also align with JNC 7.[4] However, JNC 8 does not comment on the inpatient population.[5,6] Despite a lack of clear recommendations, anecdotally, asymptomatic HTN in the hospitalized setting is at times treated with intravenous (IV) antihypertensives. Hospitalized patients may encounter transient BP elevations due to any number of causes, regardless of the presence of pre-existing HTN. One major reason may be inappropriate medication reconciliation on admission, resulting in patients being acutely withdrawn from chronic antihypertensive therapy or inappropriate dosing.[7] Due to more frequent vital assessments, hospitalized patients may have these elevations detected and reviewed.

‘Pager fatigue’ has been a growing concern that may explain the prevalence of IV antihypertensives, wherein a clinician will order an ‘as needed’ (PRN) antihypertensive to control the BP and limit frequent pages or similar communications throughout a shift.[8] This practice can be particularly concerning if repetitive in nature, without establishment of underlying chronic BP control. IV antihypertensives may be chosen over PO antihypertensives due to their quicker onset in patients with already established lines. Labetalol and hydralazine are commonly used agents for this purpose due to their low cost, wide availability, and limited contraindications. These medications can be used separately or together, keeping in mind the risk of reflex tachycardia caused by the systemic vasodilation seen with hydralazine.[9]

The choice of IV administration may be due to several circumstances surrounding a patient’s individual needs, including lack of enteral access or perceived urgency of effect needed in the clinician’s eyes. However, their use in this setting may not be completely benign. The degree of

BP reduction after administration of IV antihypertensives is likely to be heterogeneous across patients, leaving possibility for hypotension and associated adverse effects. The initial goal BP reduction in the setting of hypertensive emergency is no more than 25% within the first hour, followed by a goal of 160/100-110 mmHg within the next 2-6 hours if the patient remains stable, then to normal over the next 24-48 hours.[3,4] While this goal is standard for hypertensive emergencies, specific evidence-based BP reduction goals for hypertensive urgency are not clearly elucidated.

Due to a paucity of clear guidance, existing primary literature may be able to identify the potential benefits/risks associated with the use of IV antihypertensives. Hence, the objective of this review was to evaluate literature examining the safety/efficacy of IV hydralazine and labetalol in hospitalized patients with non-emergent, asymptomatic HTN.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10]

Literature search strategy

PubMed, Embase and Scopus databases were systematically searched for all relevant publications between the start dates of each respective database through May 2020. The search terms and strategy were compiled through investigator literature search and consultation of a medical librarian regarding the search strategy. The initial search strategy was composed in PubMed and subsequently translated to the other databases, using an iterative process to revise all searches based on new term discovery (**Appendix A**). The primary searches conducted in each database used controlled search terminology that combined three main groupings of search terms: (1) target drugs (e.g., *labetalol, hydralazine*), (2) management of HTN (e.g., *blood pressure, hypertension, hypotension*), and (3) inpatient setting (e.g., *inpatients, hospitalization, hospital medicine*). A fourth set of terms related to pregnancy (e.g., *pregnancy, preeclampsia, postpartum period*) were incorporated as *a priori* search exclusions. In addition to the primary database searches, bibliographies of identified clinical guidelines and review articles were also queried for additional studies related to the research objectives.

Four PharmD student researchers executed the final searches (**Appendix B**) in the three electronic databases, supervised by two faculty researchers with clinical/methodological expertise. Search results from all databases were exported to EndNote X9.2 (Clarivate Analytics; Philadelphia, PA), where duplicates were manually identified and removed. The remaining citations entered a series of screening stages, conducted in the DistillerSR web application (Evidence Partners; Ottawa, Ontario), detailed below.

Inclusion/exclusion criteria

English-language articles were included in the review if they evaluated the utilization of IV hydralazine and/or labetalol for the treatment of elevated BP in a hospital-based setting and provided outcomes specific to these therapies and routes. Articles were excluded if they exclusively studied any of the following patient populations: children/adolescents, oncology,

hypertensive emergency/malignant HTN (specifying end-organ damage), pregnancy/postpartum, stroke (ischemic/hemorrhagic), elevated intracranial pressure, aortic dissection/aneurysm, perioperative/peri-procedural settings, heart failure, pulmonary HTN, HTN secondary to drug misuse, dialysis, or pheochromocytoma. These populations were excluded to isolate an uncomplicated, asymptomatic patient population experiencing elevated BP in the general inpatient setting, not obviously connected to a relevant causative clinical condition. Exceptions were made in cases where data from excluded populations was stratified from included populations. For example, if a study included data for both PO and IV antihypertensives, the study was included in the review if the data for IV antihypertensives was reported separately. Articles were also excluded if they were categorized as any of the following publication types: clinical guideline, review article, commentary/editorial, thesis/dissertation, preprint publication, conference abstract, ongoing clinical trial, animal study, or case reports/series. Finally, the following studies were excluded from the review: studies that intentionally withheld maintenance medications to induce HTN; tested escalating doses in a laboratory setting; solely reliant on qualitative methodology and/or self-reported outcomes measurements; and pharmacokinetic (PK)/pharmacodynamic (PD) studies.

Data screening and extraction workflow

Forms were created in DistillerSR to assist with record screening and to ensure an objective assessment process. For both title/abstract and full-text reviews, each record was processed by two student researchers. For title/abstract screening, conflicts between researcher assessments were passed to the next stage of review, while for full-text screening, conflicts were discussed and resolved across the entire research team (inclusive of faculty leads). Full-texts identified for review were obtained utilizing available resources, including interlibrary loan, when appropriate. For the final full-texts identified for inclusion, data was extracted fully by a single student researcher, with a secondary student researcher reviewing and verifying the resulting extraction. The following data was extracted: author, year, country, study design, purpose, methods, study population, conclusions, and limitations. Quality of studies was evaluated qualitatively by the research team due to the varying study designs included in the review.

Results

A total of 4641 articles were identified in the initial search results, with 3362 remaining after removal of duplicates. The title/abstract screen resulted in 287 articles assessed in the full-text screening for eligibility. A total of 277 publications were excluded at this stage, for various reasons detailed in **Figure 1**. The final result set included 10 articles for qualitative synthesis.[8,11-19]

Summary of included studies

Out of 10 articles identified through the systematic review process, nine (90%)[8,11-14,16-19] were conducted in the United States, and one (10%)[15] in Switzerland. The publication dates ranged from 1984 to 2019, with three (30%)[15-17] published in the 1980s and seven (70%)[8,11-14,18,19] published from 2010-2019. Five studies (50%)[8,11-14] evaluated both labetalol and hydralazine, four (40%)[15-18] focused on labetalol alone, and one study (10%)[19] on hydralazine alone. The study designs of identified articles were diverse, including five retrospective cohorts (50%),[8,11-

[13,18] two prospective cohorts (20%),[16,19] two open-label experimental studies (20%),[15,17] and one quasi-experimental study (10%).[14] A total of seven studies (70%)[8,13,15-19] focused on outcomes according to a predefined BP goal, eight studies (80%)[8,11,13,14,16-19] reported adverse events, four (40%)[8,12,14,18] reported length of stay (LOS), one study (10%)[11] evaluated return visits to the emergency department (ED), and one study (10%)[11] evaluated mortality.

Details of individual studies

Labetalol and hydralazine

A retrospective cohort study by Miller C *et al*.[8] (n=1071) determined the indications and prevalence of labetalol, hydralazine, and metoprolol as PRN orders in acute care/orthopedic surgery service patients. A total of 114 patients (10.6%) received a total of 552 PRN drug administrations. The most commonly ordered IV antihypertensive was labetalol (59.6%), while hydralazine comprised 27.8% of the doses administered. A total of 21% of orders used IV antihypertensives for systolic BP greater than 180 mmHg, 46% for systolic BP 160-179 mmHg, 17% for systolic BP 140-159 mmHg, 11% for systolic BP 120-139 mmHg, 4% for “tachycardia,” and 1% for “HTN.” A total of 72.3% of administrations achieved the targeted PRN threshold within two hours of drug delivery. The median LOS for patients was nine days (range 0-58 days). Two drug administrations were associated with hypotension (systolic BP <90 mmHg) and 10 administrations with bradycardia (heart rate [HR] <60 beats per minute [bpm]).

Miller J *et al*.[11] (n=357) performed a retrospective cohort study that assessed patients that received one dose of either drug in the emergency department (ED) to determine appropriateness of IV antihypertensive use. A total of 88.2% of patients that presented to the ED had a known HTN diagnosis. Treatment was considered inappropriate if the patient: (1) received therapy for uncontrolled chronic HTN, (2) had no targeted work-up for HTN, (3) was discharged from the ED/admitted to the hospital without any HTN-related diagnoses, or (4) was admitted for HTN but no symptoms of end-organ damage. A total of 35.6% of patients received doses considered inappropriate, with the most common diagnosis being uncontrolled HTN (40.9%). A total of 29.1% of patients inappropriately treated were discharged from the ED with no work-up. There was no difference in in-hospital mortality (2% vs 0%) or 30-day ED revisit rate (18.3% vs 17.3%) between those that were treated appropriately versus inappropriately, respectively. Hypotension requiring pressor support occurred in two patients who were treated inappropriately, while one patient treated appropriately developed hypotension but did not require pressor support.

Weder *et al*.[12] (n=2189) conducted a retrospective cohort study that evaluated the use of low-dose hydralazine and labetalol (defined as 10-20 mg for each drug) PRN orders. Patients were excluded if they had a principal diagnosis of HTN or were specifically admitted for the treatment of HTN. A total of 870 patients (39.7%) had PRN orders that were never administered. In general, patients who received IV antihypertensives had a longer LOS compared to those who had an order for the IV antihypertensive but did not receive a dose. Specifically, patients who received hydralazine had a LOS ± standard deviation (SD) of 12.0 ± 15.9 days compared to 7.1 ± 9.0 days in those who did not ($p<0.001$), while patients receiving labetalol had a LOS of 11.8 ±

16.1 days compared to 7.9 ± 10.4 days in those who did not (p<0.001). Among treated patients, the mean ± SD number of doses was 5.3 ± 8.2 for hydralazine and 5.6 ± 7.7 for labetalol. A total of 64 patients (2.9%) had admission diagnoses congruent with indication for aggressive antihypertensive therapy (defined as hypertensive encephalopathy, cerebral vascular accident/infarction, subarachnoid hemorrhage, acute left ventricular dysfunction, acute pulmonary edema, or aortic dissection).

Another retrospective cohort study conducted by Lipari *et al*.[13] (n=246) evaluated prescribing practices and outcomes of IV hydralazine, labetalol, metoprolol, and enalaprilat among non-critically ill patients. Of the 321 orders prescribed, 95.7% were either hydralazine or labetalol and 56% contained PRN BP parameters for administration. Of these, 84.5% had a PRN BP threshold of <180 mmHg. Among patients receiving IV antihypertensives (n=172), intensification of the inpatient oral medication regimen occurred in 52%. A total of 32.6% experienced excessive BP lowering (>25% in six hours) and 4.7% of patients required treatment for this lowering. Specifically, among patients receiving hydralazine, 4.4% experienced increases in HR >20 bpm.

Pasik *et al*.[14] (n=260) performed a quasi-experimental study focused on appropriateness of orders and adverse events. This study described prescribing practices and prevalence of adverse events before and after implementing an institutional education initiative focusing on proper prescribing practices for IV antihypertensives. Inappropriate antihypertensive orders were defined as those prescribed to patients without symptoms of hypertensive emergency or nothing by mouth (NPO) status. After initiative implementation and assessment of 260 orders pre- and post-intervention, there was a 60% overall reduction in inappropriate IV antihypertensive orders (8.3 to 3.3 orders per 1,000 patient days, p=0.0099). A total of 33.1% of orders were associated with adverse events, almost uniformly of which were hypotension (defined as >25% decrease in BP). The initiative was associated with a decrease in these adverse events of 57% (4.4 to 1.9 antihypertensive-related adverse events per 1,000 patient days, p=0.0112). LOS was similar pre- and post-intervention at 14.8 vs 15.4 days (p=0.0769), respectively.

Labetalol alone

A prospective study by Morel *et al*.[15] (n=10) evaluated the number of labetalol doses required to achieve a reduction in BP based on the patient's rate pressure product (RPP) to achieve a goal RPP <2000 (RPP=HR x systolic BP). Patients included were admitted during a post-traumatic period to a surgical ICU and were intubated and mechanically ventilated; they were given 20 mg of labetalol and if their RPP was >2000 after the first dose, 40 mg was administered. If the RPP was still above 2000, an 80 mg dose was administered and repeated until a maximum dose of 300 mg or an RPP <2000. This protocol was performed as part of standard treatment of these ICU patients. Nine patients (90%) required two doses, seven (70%) required three doses, and three (30%) required four doses. There was a significant decrease in systolic BP (-16.2%) and diastolic BP (-8.2%) after one dose (p<0.01). After three doses, there was a cumulative decrease in systolic BP of 24.9% and diastolic BP of 16.5% (p<0.01). However, no significant reduction was found after the fourth dose.

Wright *et al*.[16] (n=14) evaluated escalating doses of labetalol via continuous IV infusion given to patients in the ED as a standard course of clinical treatment. The first eight patients received a 2 mg/min initial dose of labetalol, but a reduction to 0.5 mg/min and subsequent titration was permitted for the remaining six patients if a "precipitous fall" in blood pressure (>20-mmHg fall in diastolic BP in any five-minute period) occurred. A total of 86% of patients reached the BP goal, defined as a 30-mmHg reduction in diastolic BP. One patient experienced symptomatic hypotension. After discontinuing the infusion, eight patients saw an increase in BP greater than 10 mmHg.

A prospective, open-label study by Huey *et al*.[17] (n=20) determined the safety of labetalol to manage BP in patients with hypertensive urgency. This study was similar in design to Wright *et al*. but used bolus doses rather than continuous infusion. Patients were administered 20 mg, 40 mg, 80 mg, and 160 mg (cumulative doses of 20 mg, 60 mg, 140 mg, and 300 mg) bolus doses of labetalol step-wise in intervals of at least 10 minutes until BP control was achieved. Therapeutic response was defined as a decrease in diastolic BP to <100 mmHg or reduction judged as adequate by the attending physician. A total of 90% of patients achieved therapeutic response, at or before administration of the maximum dose of 300 mg. No episodes of tachycardia, bradycardia, or hypotension were observed. Significant decreases were seen in both systolic BP (-30 mmHg) and diastolic BP (-22 mmHg) from baseline (both $p<0.05$). Despite the small sample size, the authors of this study concluded that IV labetalol administered as small bolus doses was safe and effective for hypertensive urgency.

Malesker *et al*.[18] (n=382) further evaluated the use of labetalol through a comparison of administration of continuous IV infusion vs bolus in critically ill patients, additionally compared to nicardipine IV bolus. BP goals were individualized for patients, and those who did not have a goal in their chart were considered a success if their BP was less than 140/90 mmHg but higher than 90/60 mmHg. There was no significant difference in the mean decrease in systolic (~21-22 mmHg) or diastolic (~12-13 mmHg) BP between treatment groups, but the proportion of patients reaching their BP goal was significantly higher with nicardipine (83%) compared to both bolus and continuous infusion labetalol (67%) ($p=0.04$). The total proportion of patients experiencing adverse events (61% vs 48%, $p=0.04$) and discontinuing the drug (22% vs 6%, $p=0.04$) was higher for labetalol compared to nicardipine, respectively. Hypotension (defined as BP <90/60 mmHg) occurred in 30% of patients receiving bolus labetalol compared with 13% of patients receiving continuous infusion labetalol ($p<0.01$). There was no difference in the frequency of bradycardia (defined as <60 bpm) or high degree atrioventricular block between drugs. Rates of hypotension were higher in patients receiving labetalol by IV bolus vs continuous infusion (30% vs 13%, $p<0.01$). Differences in LOS in the ICU and overall hospital LOS were not significantly different between the groups.

Hydralazine alone

A prospective observational study conducted by Campbell *et al*.[19] (n=94) identified hospitalized patients with an order for IV hydralazine. The goal of this study was to evaluate the use of IV hydralazine (before and two hours post-administration), including the frequency, BP threshold

for ordering the drug, and degree of adverse events. Only 2% of patients had evidence of hypertensive emergency reported, and only 7.5% of patients had a physician evaluation prior to their dose. Among 201 doses, the mean ± SD BP at baseline was 175/82 ± 25/16 mmHg, reduced by 24/9 ± 29/15 mmHg post-administration. A total of 83% of patients who received hydralazine failed to achieve a >25% reduction in BP after the initial two-hour treatment period; such a reduction was significantly associated with a higher systolic BP at baseline (p=0.017). Adjustment of PO antihypertensives occurred in 25% of patients within 24 hours of hydralazine. A total of 8% of doses resulted in an adverse event, the majority being hypotension (69%), defined as systolic BP <100 mmHg or a reduction in systolic BP >20 mmHg with symptoms.

Quality of included studies

Three studies (Campbell *et al*.,[19] Huey *et al*.,[17] and Miller J *et al*.[11]) identified small sample size as limitations to their analyses. Campbell *et al*.[19] identified their small sample size as preventing the observation and assessment of less common, more severe adverse events, such as stroke. Two additional studies (Wright *et al*.[16] and Morel *et al*.[15]) did not specify such a limitation, but each included less than 15 patients in their samples. Five of the ten studies (Lipari *et al*.,[13] Malesker *et al*.,[18] Miller C *et al*.,[8] Miller J *et al*.,[11] and Weder *et al*.[12]) were retrospective in design, increasing the possibility of bias in data collection and analysis. Eight studies (80%)[8,11-14,16,18,19] were observational in nature. Three studies evaluated drugs other than hydralazine and labetalol. A total of 12.6% of doses administered in Miller C *et al.*[8] were metoprolol, while 4.4% of doses administered in Lipari *et al.*[13] were metoprolol. For Miller J *et al*.,[11] 1.6% of patients received at least one dose of metoprolol and 11% received at least one dose of enalaprilat. Those articles did not separate the data for each drug, so the inclusion of drugs other than those that were the focus of the review could have influenced the results of those studies and subsequent applicability to this systematic review. Finally, all of the studies included in the review were single-center analyses, limiting their external validity and general applicability to the average patient in other institutions.

Discussion

This systematic review identified studies raising potential concerns with the safety/efficacy of IV hydralazine and/or labetalol for the treatment of asymptomatic hypertension. Hydralazine is a potent vasodilator of arterioles, which results in decreased systemic resistance. However, dose-response to hydralazine is largely unpredictable, which can result in an unpredictable effect on BP.[9] Likewise, our review indicates variable hemodynamic effects, with some patients experiencing episodes of hypotension, and others failing to have a sufficient response. Labetalol, on the other hand, was associated with slightly more reliable hemodynamic effects, as evidenced by Morel *et al*. and Wright *et al*. studies showing a more consistent dose-response in lowering of BP. Labetalol has negative chronotropic effects due to binding to cardiac beta-1 and beta-2 receptors, causing the reduced HRs.[20] These effects may be a concern in some patients since bradycardia was found to be a common adverse effect of therapy.[20] The alpha- and beta-blocking profile of labetalol makes it a good candidate for the lowering of acute BP elevations, but its use may be unnecessary in asymptomatic HTN.

The evaluation and impact of both drugs on outcomes beyond vital assessments was an important finding of this review. Weder *et al*.[12] found a significant increase in the overall LOS for patients receiving either labetalol and hydralazine. As longer hospitalizations increase costs, as well as the risk of nosocomial and other complications,[21] this impact is important to identify. In this study, the patients in the IV treatment group were significantly older than in the non-treatment group, which may have contributed to the increased LOS, but other comorbidities and characteristics did not differ between the groups.[12] The other studies assessing LOS[8,14,18] found limited to no association with IV antihypertensive treatment, nor did Miller J *et al*[11] in their assessment of ED return visits or mortality. While it appears that the impacts of IV antihypertensive therapy may not broadly alter these healthcare utilization outcomes, the studies did indicate a clear trend for an increased risk of adverse events. This almost uniformly consisted of hypotension, which in several cases required intervention and/or drug discontinuation. This finding represents an important outcome to assess for future experimental studies.

One concerning finding of the Campbell *et al*.[19] study was the general lack of patient evaluation by the prescriber prior to administration of an IV antihypertensive. The authors speculated that the clinical decision-making for the choice of IV hydralazine was likely due to unfamiliarity of physicians and nurses with the guidelines for asymptomatic HTN vs hypertensive emergency; many of these orders were placed by physicians in training, though many other unknown factors may have contributed to this practice as well. As demonstrated by Pasik *et al*.,[14] educational initiatives for IV antihypertensives can encourage protocol-based prescribing to narrow use to when it is clinically indicated. While mainly anecdotal, the concept of ‘pager fatigue’ may come into play. The most common clinicians paged in response to out-of-range clinical values are likely to be interns and/or residents, which might promote the prevalence of PRN antihypertensives. Due to the high patient census a physician may be responsible for, the temptation to ‘treat the number’ to silence a pager may be a contributor to this issue. Regardless of the reasoning behind the orders, clinical education on the appropriate use of IV antihypertensives may be a useful tool for future work to implement and utilize.

The JNC 7 guidelines emphasized a lack of evidence that “*failure to aggressively lower BP in the ER is associated with any increased short-term risk to the patient who presents with severe hypertension*.”[3] Practically, evaluating the safety/efficacy of IV antihypertensives may be useful for patients that lack enteral access or other circumstances where IV is the only appropriate route of administration. However, the data presented in this review was not specific to this circumstance. There have been studies focusing on outpatient management, such as the one performed by Patel *et al*.[22] that studied 59,836 patients with hypertensive urgency. In this large cohort, patients referred to the hospital for treatment had more major adverse cardiovascular events at seven days ($p=0.02$) than those treated as outpatients. Further evidence is required to definitively draw a conclusion about the safety of inpatient management of asymptomatic HTN.[22]

A prospective comparison of IV and PO antihypertensive medications focusing on the safety and efficacy of the drugs being compared, such as systolic and diastolic BP measurements and adverse events, is currently lacking in the literature. Comparing the IV and PO formulations of

the same drug would allow a better comparison than the inclusion of multiple drugs as seen in several of our included studies. Since labetalol tends to be more consistent in its BP-lowering effects and predictability in comparison with hydralazine, an IV vs PO comparison would be valuable. A similar analysis for hydralazine would also be clinically beneficial, particularly to advise use in patients with contraindications to beta blockers.

Although this review was able to identify some useful trends across the literature, one limitation was the heterogeneity of the included studies. The focus of studies ranged from BP outcomes to adverse event to changes in prescribing practices. The majority of these studies also noted safety and blood pressure as the main clinical outcome with the only additional efficacy outcome being LOS. Some studies included IV antihypertensive agents outside the focus of the review, such as nicardipine, metoprolol, and enalaprilat, though these numbers were very low and thought to not significantly impact the results of the review. Hence, only a qualitative analysis of studies and potential bias was possible and not a quantitative analysis. The goal of this review was to focus on the specific clinical scenario where limited evidence justifies the use of these therapies; as such, it did not review the use of these agents for other indications, even though those may have commented on adverse effects or blood pressure-lowering properties. With this in mind, the generalizability of this analysis to utilization with other indications may be limited. Finally, some full-texts were unable to be obtained or reviewed through the review process due to language differences or inability to obtain the article, so it is possible that relevant studies were not included in the systematic review.

Conclusion

This systematic review of the safety/efficacy of IV hydralazine and labetalol for management of asymptomatic HTN in hospitalized patients found that while the literature is limited on this subject, IV antihypertensives should be used with caution in this patient population until further evidence emerges. Due to potentially unpredictable effects on BP, potential for adverse effects, and the lack of outcome-based efficacy data, further investigation on the safety and efficacy of these drugs is warranted. While recent guidelines that address non-emergent HTN currently recommend oral antihypertensives, clinical situations may arise where the treatment of asymptomatic HTN is required for patients in whom enteral intake is contraindicated. Therefore, the clinical implications and potential risks of the utilization of intravenous antihypertensives for non-emergent HTN warrant further investigation.

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Tables

Table 1: Extracted details of included studies evaluating the safety/efficacy of hydralazine and/or labetalol

Author, year, country	Study objective	Patient population/setting	Methods	Main findings	Limitations
Miller C (2012) [8] United States	Characterize the prevalence, indications, and cost of short-acting IV antihypertensive therapy for acute HTN in surgical patients; hypothesized that such therapy is associated with significant cost despite no proven benefit	n=1071; median age (range): 54.5 (19-91); male (65.8%); median (range) LOS: 9 (0-58); HTN (55.1%)	Query of pharmacy administration database for patients who had received intermittent, PRN orders of IV hydralazine, metoprolol, and/or labetalol during the study period	10.6% of acute care surgery and orthopedic surgery patients received a total of 522 PRN antihypertensive drug administrations; 55.1% of patients had a pre-existing diagnosis of HTN upon admission; of these patients, 76.3% were started on their home medication(s) during their stay in addition to receiving PRN therapy; for those patients without a preexisting HTN diagnosis, only 13.3% received a diagnosis of HTN upon discharge; only 18.2% were discharged on new antihypertensive medications; Breakdown of indications for PRN antihypertensives: (SBP >180 mmHg: 21%; 160-179 mmHg: 46%; 140-159 mmHg: 17%; 120-139 mmHg: 11%; tachycardia: 4%; HTN: 1%); for PRN use, labetalol (10 to 20 mg) was prescribed most often (59.6% of doses); hydralazine was also commonly used for acute HTN (27.8%), whereas metoprolol was used less frequently (12.6%); due to the half-life and duration of action of hydralazine, a higher number of doses/patient were seen with this agent compared with the other agents studied; only 72.3% of drug administrations achieved the target PRN threshold within two hours of drug delivery	Clinical decision making for choice of agent not assessed; extrapolation of evidence on treatment of hypertensive emergencies; impact of "pager fatigue" not assessed
Miller J (2017) [11] United States	Characterize the appropriateness of bolus IV administration in ED patients with elevated BP	n=357 (n=230 documented or suspected emergency); age: 18-98 (mean 55) years; race: African American (93%); known underlying chronic hypertension (88.2%)	Identified patients using pharmacy records for patients in the ED that received at least one IV bolus dose of labetalol, hydralazine, enalaprilat, or metoprolol; retrospective chart review stratified patients into appropriate and inappropriate orders according to ED documentation of hypertensive crisis	64.4% of patients received appropriate treatment for suspected or confirmed hypertensive emergency; patients deemed to have received inappropriate orders had an average BP of 176/90 30 minutes after treatment and 172/97 60 minutes after treatment; no difference in mortality in patients treated appropriately (2%) vs. inappropriately (0%); rate of 30 day ED revisits were equivalent appropriate (18.3%) vs. inappropriate (17.3%); hypotension occurred in two patients treated inappropriately for elevated BP, requiring vasopressor support; hypotension occurred in one patient treated for hypertensive emergency	Small sample size; single study site; data limited by available documentation

Weder (2010) [12] United States	Evaluate the use of low-dose IV hydralazine (10-20 mg) in patients admitted to the hospital with primary diagnoses other than HTN	n=2189 (no drug administered [n= 870]; hydralazine and labetalol [n= 412]; hydralazine only [n= 581]; labetalol only [n= 326])	Query of the hospital's electronic data warehouse was made to identify patients in the study period who had orders written for IV labetalol and/or hydralazine; patients received IV hydralazine 10-20 mg or labetalol 10-20 mg as a bolus or PRN dose	LOS was longer in patients who received IV antihypertensives vs those who did not; LOS for patients for whom hydralazine was ordered and who received at least 1 dose was 12.0 ± 15.9 days but only 7.1 ± 9.0 days for those who did not receive a dose ($p<0.001$); LOS for patients who received labetalol was 11.8 ± 16.1 days vs 7.9 ± 10.4 days for those who did not receive a dose ($p<0.001$)	Very limited initial analysis of how and why hypertension is managed in the in-patient setting; to better understand practice it will be important to determine use of drugs and BP thresholds beyond a single center; costs associated with in-patient pharmacologic treatment
Lipari (2016) United States	Determine the frequency of prescribing and administering episodic IV antihypertensives and outcomes	n=246 (had order but did not receive dose [n=74], received dose [n=172]; hydralazine (80.1%), labetalol (15.6%), metoprolol (4.4%), enalapril (0%)	Patients who had an order and received an IV antihypertensive were compared with patients who had an order for an IV antihypertensive but never received a dose	Of the 172 patients who received IV therapy: 48% received 1 dose, 26% received 2 doses, 11% received 3 doses, and 1 patient received 10 doses; majority of orders containing SBP criteria for administration of an episodic IV antihypertensive agent were well below the BP level associated with immediate or near-immediate cardiovascular risk; BP parameters for administration were included in 56% of the orders, 84.5% of those had a BP threshold of <180 mmHg; adverse events: 32.6% of patients had BP reductions >25% in six hours; excessive BP reductions in 4.7% of patients which required treatment (IV fluids: two patients (1.2%); held scheduled PO med: six patients (3.5%)); of the patients who received IV hydralazine, 4.4% had an increase in HR >20 bpm, with seven having a HR >100 bpm; one labetalol patient experienced bradycardia	Single center study not generalizable; findings depended on accuracy of medical record; necessary data missing from medical records; impact of acuity of illness and concomitant disease not addressed; all outcomes measured were short-term; long-term BP control, rehospitalization rates, or morbidity and mortality not assessed
Pasik (2019) [14] United States	Decrease the number of inappropriate orders (without symptoms of hypertensive emergency or order for NPO) of IV antihypertensives and adverse events associated with IV orders	n=260 orders (pre-intervention [n=127]; post-intervention [n=133])	Protocols were implemented in attempt to decrease the number of inappropriate orders (staged provider quality improvement intervention to educate on use of IV labetalol and IV hydralazine use; EMR advisory warnings placed on antihypertensive orders of labetalol and hydralazine; patient's charts who had written orders for IV	Overall 60% reduction in inappropriate IV antihypertensive orders/1,000 patient days; adverse events decreased 57% per 1,000 patient days; inappropriate orders decreased from 8.3 to 3.3 orders per 1,000 patient days ($p=0.0099$); adverse events associated with IV antihypertensives decreased from 3.7 to 0.8 per 1,000 patient days ($p=0.0072$); there were 86 adverse events (33.1%), the majority of which (94.2%) were a >25% decrease in BP, 7% bradycardia, 2.3% tachycardia, 2.3% symptomatic dizziness; overall, there were 76 orders (29.2%) with documented alternate etiologies (22 anxiety, 38 pain,	Only BP elevations associated with IV antihypertensive order were examined; documentation limited by availability in medical record; would have liked to conduct an interrupted time series analysis to assess effect of intervention over time, insufficient orders to

			antihypertensives were retrospectively reviewed and evaluated following each stage of education intervention); data was collected before and after the implementation of these interventions	five steroids, one withdrawal, 10 off home antihypertensives); the number of orders per 1,000 patient days with an alternate etiology decreased from 4.7 in the pre-intervention period to 1.2 post-intervention (p=0.0044); as a balancing measure, 111 patients with elevated BP were monitored for adverse events during the post-intervention period; among patients who did not receive IV medication based on the algorithm, there were no adverse events	perform such analysis
Morel (1984) [15] Switzerland	Evaluate the cardiovascular effects of incremental fixed IV doses of labetalol in patients presenting a "hypertension-tachycardia syndrome" in the post-traumatic period	n=10; median age: 43 ± 20 years; mean weight: 72 ± 20 kg; CVP: 0.9 ± 0.29; days after trauma: 4.1 ± 1.6 days	Protocol: labetalol was administered at 20 mg over 15 minutes (average 2.1 ± 1.2 mg/kg); after five minutes, RPP was > 2000, 40 mg of labetalol was given; if RPP was still > 2000, 80 mg of labetalol was given; 80 mg doses were given until a max of 300 mg was reached or RPP was below 2000	90% of patients needed second dose, 70% needed third dose, and 30% needed fourth dose; significant decrease in SBP 16.2%, DBP 8.2%, MAP 12%, and HR 12% after first dose (p<0.01); significant decrease in SBP 24.9%, DBP 16.5%, MAP 21.4% after third dose (p<0.0001); no significant reduction in SBP, DBP or HR after fourth dose; 2 hours after administration, SBP rose significantly (10%; p<0.05) and remained for 24 hour follow up, no significant change in HR	None documented; small sample size; no comparison group; all patients intubated and mechanically ventilated
Wright (1986) [16] United States	Describe their experience with the drug (labetalol) administered by IV administration	n=14; age: 29-73 years; sex: female (7, 50%), male (7, 50%); race: African American (10, 71%), Caucasian (4, 29%)	BP management protocol: 2 mg/min IV infusion (first 8 patients) then modified to allow reduction to labetalol 0.5 mg/min IV when fall in BP exceeded 20 mmHg diastolic during any 5 minute period; Once BP recovered rate for 15 min increased to 1 mg/min and then after an additional 15 min increased rate to 2 mg/min	Goal BP achieved in 86% of patients; patients 1-8 received 2 mg/min labetalol throughout treatment period; patients 1-6 continued infusion after reaching goal BP, BP continued to decrease but none of the patients became hypotensive (lowest BP 122/84); one patient became symptomatic when BP was lowered from 250/154 to 130/92 in 30 mins, symptoms resolved when infusion D/C; BP increased > 10 mmHg within 10 minutes of d/c infusion in 8 patients, in 2 patients it took 18 hours; no correlation between duration of hypotensive action and total dose of labetalol received; the study suggests that doses in package insert labeling (2 mg/min) may be too high	None documented; small sample size; change in protocol mid-study; some patients in hypertensive emergency
Huey (1988) [17] United States	Evaluate the efficacy and safety of IV boluses of labetalol in the treatment of patients presenting to the hospital with a diagnosis of hypertensive urgency (DBP 110 mmHg or	n=20; age: 42-71 (mean 55) years; sex: male (100%); race: African American (60%), Caucasian (40%)	Protocol: 20 mg dose injected IV over 2 minutes; additional doses of 40, 80, and 160 mg (cumulative doses of 20, 60, 140, and 300 mg) were administered at intervals of at least 10 minutes each in a stepwise fashion as needed to control BP (control defined as	90% of patients responded after receiving up to 300 mg of labetalol (mean dose to response 82 ± 20 mg); DBP: reduced from 120 ± 2 mmHg at baseline to 98 ± 2 mmHg following the last dose of labetalol (p<0.05); 70% of patients exhibited a decrease in DBP of 20-40 mmHg; 20% of patients exhibited DBP decreases between 12-19 mmHg; SBP: decreased from 185 ± 3 mmHg at baseline to 155 ± 4 mmHg following the last dose of labetalol (p<0.05); 85% of patients exhibited a	Physician discretion of dosing interval effected time to response definitive conclusion made off of small sample size

	greater) in terms of the time required for BP control, efficacy, and the occurrence of adverse events		DBP < 100 mmHg or reduction judged adequate by the physician) or until max dose of 300 mg administered	decrease in SBP of 20-45 mmHg; 15% of patients had decrease in SBP of 10 mmHg or less; median time to BP control was 30 minutes (range 7 to 110 minutes); no significant change in HR; ADR: no episodes of tachycardia, bradycardia, or hypotension	
Malesker (2012) [18] United States	Evaluate the short term clinical outcomes and costs of IV labetalol and nicardipine in critically ill patients	n=382 (labetalol [n=189]: 54% male, nicardipine [n=193]: 55% male)	Group one received labetalol bolus (average dose 13.7 ± 6.2 mg/h); group two received nicardipine (average dose 7.1 ± 5.6 mg/h)	No significant differences in the average change in SBP (p=0.79) or DBP (p=0.82) between labetalol and nicardipine; patients achieving their BP goal was significantly higher with nicardipine (83%) than with labetalol (67%) (p=0.04); patients requiring conversion to another antihypertensive agent was significantly greater with bolus labetalol (44%) compared with continuous infusion labetalol (24%) (p=0.01); total number of adverse events was higher in the labetalol group (61%) than with nicardipine (48%) (p=0.04); hypotension was significantly higher in patients who received bolus labetalol (30%) compared to continuous infusion (13%) (p<0.01); the number of patients discontinuing labetalol (22%) was significantly higher than nicardipine (6%) (p=0.04); switch to PO antihypertensive, time to initiation of PO antihypertensive, LOS in ICU, and total LOS were not significant between the two groups	Data collected retrospectively; statistical comparison failed to demonstrate significant differences when large number of demographics and clinical characteristics considered; lack of randomization and blinding may introduce bias
Campbell (2011) [19] United States	Evaluate the use of IV hydralazine at their institution in non-intensive care or obstetric settings including: frequency of off-label use, the BP threshold for which the drug was ordered, the incidence, type, and severity of adverse events, and the regularity of physician evaluation for parenteral antihypertensive drug requirements as well as post-treatment follow-up	n=94; age: 69 ± 18 years; sex: female (48%), male (52%); chronic hypertension (89%), hypertensive emergency (4%); baseline BP: 175/82 ± 25/16 mmHg	Patient charts were reviewed for the following: mean BP prior to administration of IV hydralazine, change in BP and HR within 2 hours post-administration, and adverse events; monitoring parameter for hypotension: reduction in SBP ranging -27 to -100 mmHg from pre-treatment	201 doses of IV hydralazine were administered (mean dose: 11.4 mg ± 4.3 mg); 49% of the doses were ordered as one-time urgent doses; 82% were ordered by physicians-in-training; 7.5% of patients were evaluated by a physician prior to hydralazine administration; two hours post-administration: mean BP reduction 24/9 ± 29/15 mmHg; HR increase: 4 ± 13 bpm; 83% of doses administered resulted in <25% SBP reduction; 8% of doses resulted in an adverse event; 69% hypotension (6 patients had >65 mmHg reduction); Degree of BP reduction: pre-treatment SBP <164 experienced modest reduction (-3±20 mmHg); pre-treatment SBP >190 experienced marked reduction (-35 ± 25mmHg); changes in BP in lowest pre-treatment range were significantly smaller than other ranges (p<0.001); patients with history of arrhythmias (p=0.021) and prior ACEI/ARB use (p=0.030) were more likely to have >25% reduction in SBP with IV hydralazine; higher pre-administration SBP was	Did not address clinical decision making behind choice of hydralazine; sample size too small to detect serious adverse events

				significantly associated with >25% reduction in BP (p=0.017)	

ACEI = angiotensin converting enzyme inhibitor; ADR = adverse drug reaction; ARB = angiotensin II receptor blocker; BP = blood pressure; CVP = central venous pressure; DBP = diastolic blood pressure; D/C = discontinue; ED = emergency department; EMR = electronic medical record; HR = heart rate; HTN = hypertension; IC = intensive care unit; IV = intravenous; LOS = length of stay; MAP = mean arterial pressure; n = number; NPO = nothing by mouth; PO = oral; PRN = as needed; SBP = systolic blood pressure

Figure 1: PRISMA flowchart for selection of studies evaluating the safety/efficacy of hydralazine and/or labetalol