**WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care**

**Worksheet author(s)**
- Thomas Nguyen, MD  
- Mount Sinai Medical Center

**Date Submitted for review:**  
- Dec 1, 2009

---

### Clinical question.

**ALS-D-022A**

In adult patients in significant bradycardia (prehospital and in-hospital) (P), does the use of any drug or combination of drugs (I) compared with not using drugs (or a standard drug regimen) (C), improve outcomes (eg. reversion rates) (O)."

**Is this question addressing an intervention/therapy, prognosis or diagnosis?** therapy

**State if this is a proposed new topic or revision of existing worksheet:** revision

---

### Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? no

---

### Search strategy (including electronic databases searched).


---

### State inclusion and exclusion criteria

**Inclusions:** Studies included those that specifically addressed the treatments of Bradycardia, including medical therapy and transcutaneous pacing. Studies that met the inclusion criteria also included those that involved Human subjects, randomized control trial, review articles, metanalysis, practice guidelines, and case studies. Review articles were used to further find referenced articles

**Exclude:** Studies that were excluded were those that involved animals, had abstracts only, and studies that did not involve specifically the treatments for bradycardia.

---

### Number of articles/sources meeting criteria for further review:

**75 articles were chosen for further review.**

Review articles, case reports with fewer than 3 subjects were eliminated but references look at.

**Standard medical treatments for Bradycardia are considered to be Atropine +/- Epinephrine or Isoproterenol.**

**Articles were essentially for treatments other than standard treatments, new articles for Atropine and transcutaneous pacing.**

**36 articles were chosen for final review.**
## Summary of evidence

### Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Evidence Supporting Clinical Question</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Level of evidence**

- **A** = Return of spontaneous circulation
- **C** = Survival to hospital discharge
- **D** = Intact neurological survival
- **E** = Other endpoint (HR, BP, and others)
- **Italics** = Animal studies
### Evidence Neutral to Clinical question

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Smith, 1994, E (atropine vs Glycopyrrolate vs control)</td>
</tr>
<tr>
<td></td>
<td>Feneck 2001, E (for Milrinone)</td>
</tr>
<tr>
<td>Fair</td>
<td>Hedges 1991,C (TCP vs control)</td>
</tr>
<tr>
<td></td>
<td>Paris, 1985, C (TCP, no control)</td>
</tr>
<tr>
<td></td>
<td>Rosenthal 1991,C (TCP, no control)</td>
</tr>
<tr>
<td></td>
<td>Rothman 1995, E (aminophylline vs control)</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 2 3 4 5

**Level of evidence**

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 2 3 4 5

A = Return of spontaneous circulation   C = Survival to hospital discharge   E = Other endpoint
B = Survival of event                 D = Intact neurological survival   Italics = Animal studies

### Evidence Opposing Clinical Question

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 2 3 4 5

A = Return of spontaneous circulation   C = Survival to hospital discharge   E = Other endpoint (increase hr, BP, etc)
B = Survival of event                 D = Intact neurological survival   Italics = Animal studies
There were not many randomized controlled trials in humans for the medical treatments of symptomatic bradycardia. Most good studies were observational studies and the case-control studies were not all randomized. Many articles involved transcutaneous pacemakers and animals.

I. The 3 questions I attempted to answer were:

Q1. Are there any new evidence in support/neutral/opposing for standard medical treatment (atropine + / - epinephrine, Dopamine) for bradycardia? What is optimum dose for Atropine?

Q2. Are there other medical treatments other than the standard in support/neutral/opposing for the treatment of bradycardia? (Mainly theophylline, glucagon, milrinone, dobutamine, others)

Q3. What is evidence for using transcutaneous pacing for bradycardia both pre-hospital and in hospital?

II. Result for question Q1:

Standard treatments: new Atropine and Dopamine study

Kovarik 2008 (LOE1, good, 199): Atropine study
This is Randomized, placebo controlled, cross over study of 24 patients to determine if Atropine can counteract the negative chronotropic effects of Fingolimod which has a 4 hr nadir for bradycardic effects. 12 subjects received oral Fingolimod concurrently or with placebo. A second group of 12 subjects received atropine/placebo 4h after the fingolimod dose. Result: see abstract. Atropine blunts the bradycardic effects of Fingolimod.
Final assessment: Atropine reversed and prevented the negative chronotropic effect of Fingolimod. The results of this study may not be applicable to the general population with bradycardia from other causes.

Morrison 2008 (LOE1, fair, 341). This RCT by Morrison involved 82 patients who had symptomatic bradycardia refractory to atropine and fluids. They were randomized to either receive TCP (transcutaneous pacing) (42 pts) or IV Dopamine (40 pts) starting at 5 mcg/min. Out comes were survival to discharge 30 days (69% for TCP and 70% for dopamine group). Both groups did equally well. This study was really to determine the feasibility pre hospital TCP, but one can indirectly observe the effects of dopamine as a potential second line of drugs in symptomatic bradycardia refractory to treatment first with Atropine and fluids. No data was reported on the HR or BP increases.

What is the optimum dose for Atropine?

There were no head to head trials on what is the optimum dose for Atropine in the treatment of bradycardia. The dose recommendation 0.5 -1mg IV is a range that was derived from several studies. The retrospective cohort study by Brady (LOE4, good, 41) used Atropine .97mg +/- .55mg prehospital and 1.2mg +/- .96 mg in hospital in 131 pts without any major complications. Chadda 1975 (LOE4, good, 158) used atropine .4mg – 1 mg range without problems too. Chadda 1977 (LOE4, good, 503) again used Atropine 0.008 mg/kg (range .4-.6mg), in addition reported that a dose >0.8mg increases the incidence of tachycardia HR>100 in this study. In the study by Swart 1999 (LOE4, Fair, 647), Atropine 1mg +/- .58mg was used pre-hospital, 1.3 mg +/- mg in the in hospital for a Total of 1.6 mg +/- 1.1 mg. Kovarik 2008(LOE1, good, 199) used Atropine .25mg titrated up to 2mg (1.5 mg +/- 0.6 mg). The study by Smith 1994(LOE1, good, 245) used Atropine .005mg /kg (.35 mg avg dose) with good results, The study by Chamberlain 1967 (LOE4, good, 12) determined that the maximal increase in HR from Atropine in healthy human subjects was about 3mg. From all the above
studies, it can be extrapolated that Atropine .5 mg -1 mg doses IV up to 3mg can be given safely pt with Bradycardia.

In a study by Brunner 1997(LOE4, fair, 1838) of 3 of 23 post heart transplant patient showed high degree AV blocks. Another study also indicated that atropine may paradoxically cause high degree AV block in a cohort of 25 patients after cardiac transplantation (LOE 5, Bernheim 2004, 1181)
The use of atropine in post cardiac transplant patient is with caution.

III. Results for question Q2:

**Theophylline/ aminophylline:** several clinical areas this drug was used are bradycardia from post MI, post heart transplant, spinal cord injuries and sick sinus syndrome


Early complications of post inferior MI are bradycardia and AV block, possibly mediated by adenosine. Methylxanthines (Theophylline or Aminophylline) may attenuate the heart’s response to adenosine and provide chronotropic support.

Alboni 1990. (LOE4,fair,supports, 1037) Alboni studied the electrophysiolgic effects of theophylline in 15 patients with bradycardia. Pts were not randominzed, was an observational study. The conclusion was that theophylline improves sinus nodal function.

Bertolet 1995. (LOE4, Fair, 123). In this observational, uncontrolled study, 8 patients with post MI AV block initially unresponsive to Atropine, responded to IV theophylline 100 mg/hr up to max. of 250 mg. Mean SBP and AV block improved in all patients.

Stradberg 1991. (LOE4, fair, 527). Similiar results were confirmed in the study by Strasberg, which was an observational, uncontrolled study of 15 consecutive patients with inferior MI who developed high degree AV blocks. Aminophylline improved the conduction rates in this population.

Goodfellow 1994. (LOE5, poor, 862). Similarly, a case series by Goodfellow reported 3 cases of inferior MI with Atropine resistant AV block that responded to IV Aminophylline, thus avoiding the need for pacing.


Another use of theophylline/aminophylline is in post heart transplant patients with sinus bardycardia and/or sinus node dysfunction.

Bertolet 1996. (LOE2, fair, 396). Bertolet, in a case-control study, nonrandomized study of 47 patients, demonstrated that theophylline 5 mg/kg given over 10 minutes reversed the bradycardia (62 +/- 7 beats/min to 89 +/-10) in post orthopic heart transplant patients.

Rothman 1995.(LOE4, fair, 429) A less robust improvement in bradycardia events was seen in the study by Rothman. This was a case- control nonrandomized study of 26 post heart transplant patients. Only 1 out 13 patients had significant improvement in sinus node abnormalities as determined by sinus cycle length and SA conduction time.


Small dose of IV theophylline may be a useful alternative treatment in bradycardia following spinal cord injury that is unresponsive to atropine. A proposed mechanism may be theophylline increases the force of contraction of diaphragmatic muscle through the enhancement of calcium uptake via an adenosine mediated channel. The bradycardic effects may be mediated by the inhibition of phosphodiesterase 3.
Schultz-Stubner 2005. (LOE4, poor, 1809) reported 3 cases of spinal cord injury patients who had symptomatic bradycardia refractory to atropine and responded to IV theophylline 200 mg bolus. All had improvements in bradycardia and ventilation.

Many similar individual cases were reported in spinal cord injury cases with symptomatic bradycardia, all with positive results. (Pasnoori 2004, Sakimoto 2007, Weant 2007, Whitman 2008). A larger prospective randomized study is needed to confirm these case reports.


The use of theophylline in this scenario is for long term use, oral dosing and may not be so pertinent to acute management of bradycardia cases.

Alboni 1991 (LOE2, good, 1361). Alboni reported in a case controlled study of 17 patients aged 66+-/11 yr with symptomatic bradycardia and sick sinus syndrome, who were given oral theophylline 700mg/ d. Improvements were seen in resting HR, 24 hr HR, exercise HR and overall decreased in symptoms of bradycardia.

Kragie 1996. (LOE4,fair, 324) Similarly, Kragie in an observational study, (no control) of 11 elderly patients who were given oral Theophylline for symptomatic bradycardia. All had positive responses to increases in HR and hemodynamic stability. Statistical analysis were not performed.

Saito 1993 (LOE4, fair, 1199) reported similar results in observational uncontrolled study of 17 elderly patients given oral theophylline for bradycardia for sick sinus syndrome.

Alboni 1993. (LOE4, fair, 1142) reported in an observational study of 17 elderly patients with atrial fibrillation with slow ventricular response that oral theophylline was an effective therapy in most of these patients.

Glucagon  Love 1997 (3 pts); Love 1998 (9pts); Doyon (1 pt)

Glucagon may have a role in the treatment of symptomatic bradycardia, particularly those with beta adrenergic blockade and perhaps calcium channel blockers. Glucagon works well in these scenarios because its action is via a different receptor site then beta adrenergic receptor. Glucagon increases cAMP and increase the influx of calcium thus increasing the automaticity of sinatrial and AV nodes as well as increasing contractility.

No controlled studies in humans have been done with glucagon on symptomatic bradycardia.

2 studies by Love have shown improvement in patients receiving IV glucagons 50 ug/kg with maintenance 1-10mg/hr.

Love 1998 (LOE4, fair, 323). In this observation, uncontrolled study of 9 patients who presented with symptomatic bradycardia refractory to initial treatment with Atropine, demonstrated an improvement in BP and HR in all 9 patients after receiving IV Glucagon. All 9 patients took oral medication that may have contributed to symptomatic bradycardia (beta blocker, calcium channel blockers, digoxin).

Love 1997 (LOE5, poor, 181) also presented a report of 3 cases that demonstrated similar effects with IV Glucagon. 2 cases involved Atenolol ingestion and 1 involved Verapamil.

Final consensus: Glucagon should be used in bradycardic patients with bradycardia from suspected drug overdose (beta blockers). RCT need to be done in the future.

Isoproterenol. Study: Kovarik1 2008

Kovarik1 2008. (LOE1, good, 199) isoproterenol

This was a randomized placebo controlled cross over study of 14 patients to study whether isoproterenol can blunt the bradycardic effects of Fingolimod, an immunomodulator for the treatment of multiple sclerosis. All
patients received infusions of isoproterenol or placebo. Results: Isoproterenol was able to increase the heart rate by 80% from base line prior to infusion of Fingolimod. When Fingolimod was added, a higher dose (41%) of isoproterenol was needed to achieve a heart rate to a range of 100-120.

Final assessment: isoproterenol increases the HR in patients and in patients with bradycardia caused by Fingolimod. The first part of the study demonstrated increased in HR from isoproterenol versus placebo. The results of this study may not applicable the general population with bradycardia from other causes.

**Phosphodiesterase inhibitor**

**Milrinone versus Dobutamine.** Study Feneck 2001.

Milrinone inhibits the phosphodiesterase isoenzyme responsible for the breakdown of CAMP thus increasing the levels of cAMP leading to the influx of calcium. This results in increased heart contractility and rate. Dobutamine also increases cAMP by binding on beta adrenergic receptors.

Feneck 2001 (LOE1, fair, supports dobutamine, neutral for Milrinone, 306). This randomized, open label, multi-centered study by Feneck compared the hemodynamic effects, efficacy, and safety of Milrinone versus Dobutamine. Although this study did not study bradycardia patients, it did show the potential use and side effects of Milrinone and Dobutamine. The study population however was post cardiac surgery patients. Dobutamine increased HR 35% and MAP by 31%. Milrinone increased HR by 10% and MAP 7%. Milrinone had higher incidence of bradycardia 13% as compared to Dobutamine 2%. Conclusions: studies should be done on symptomatic bradycardic patients. Dobutamine and Milrinone may have the potential to treat bradycardia by increasing heart rate, blood pressure and cardiac index. Final consensus: Both drugs are good for low cardiac index patients. Dobutamine seems to be slightly better than Milrinone and less bradycardic effects.

Atarashi 2004 (LOE4, good, 534). Cilostazol is another phosphodiesterase inhibitor studied by Atarashi, et al. This was a prospective observational study of 20 patients: 8 with bradycardic atrial fibrillation, 8 with sick sinus syndrome and 4 with Wenckebach type AV block. Holter monitoring was used to measure heart beat before and 2 weeks after oral administration of daily Cilostazol 200 mg. See abstract for results. Cilostazol had a positive chronotropic effect in patients with bradycardia. Final consensus: Cilostazol is a novel drug, not used routinely in clinical setting for ALS.

**IV. Result Q3: Transcutaneous pacing (TCP) for bradycardia**

Studies involving TCP for symptomatic bradycardias are lacking. Most studies are for combined asystolic, bradycardic arrest. The efficacy for TCP is generally poor for both prehospital and inhospital patients bradyasystolic arrest.

Evidence for the efficacy of TCP for prehospital bradycardia patients is indeterminate. A. The majority of the studies on prehospital TCP involve bradyasystolic arrest and therefore not applicable. Three studies involved prehospital TCP for symptomatic bradycardia. The first study by Hedges in 1991 (LOE2, fair, 1473) showed that prehospital TCP for bradycardia showed a slight increase in survival to discharge (4/27) versus control (0/27), although not significant. All patients did receive standard ACLS care including medical treatments of epinephrine and atropine. A second study by Barthell (LOE2, Fair, 1221), a subgroup analysis of a bigger study, showed survival to discharge in 5/6 patients in the TCP treatment group vs 1/7 in control. Lastly, a subgroup analysis of 8 bradycardic patient in a study by Paris- (LOE4, fair, 320) showed 0% survival and 0% TCP capture. The combination of the 3 studies showed 22% (9/41) survival to discharge in TCP group versus 3% (1/34) in control groups.

Inhospital patients who got TCP for symptomatic bradycardia seemed to have slightly better rate of capture (Sodeck-LOE4, fair, 96)(Zoll-LOE4, Fair, 937) and better survival to discharge rates (18-75%)(Clinton-LOE4, Fair, 155), (Vokov-LOE4,fair, 738)(Rosenthal-LOE4, Fair, 2160) than prehospital patients (22%). This is likely to confounded by multiple factors including getting TCP earlier and being in a more controlled environment.
Inhospital patients generally will get transvenous pacing also. Early TCP resulted in better outcomes. (Zoll-LOE4, Fair, 937)

The evidence for medical treatments versus TCP is very limited. A RCT of 45 patients by Smith 1994 LOE1, good, 245) comparing Atropine, glycopyrolate and TCP in intraoperative patients showed no significant differences, all groups showed a period of recurrent bradycardia in about a third of their patients. The TCP group overall showed more consistent HR though. A feasibility study by Morrison 2008 (LOE, Fair, 341) compared Dopamine versus TCP in bradycardic patients refractory to Atropine. There were no differences in outcomes of survival to discharge. (69% versus 70%)

Acknowledgements:

Citation List

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td></td>
</tr>
</tbody>
</table>
LOE 4: good, supports. 20 patients, observational, no control. Followed for 2 weeks. |
LOE4, fair, supports. Observational 24 pts, 19 with bradycardia. Inhospital TCP |
LOE2, fair, favors. Subanalysis 13 pts with symptomatic bradycardia |
| Bernheim 2004 | Bernheim A. Atropine often results in complete atrioventricular block or sinus arrest after cardiac transplantation: an unpredictable and dose-independent phenomenon. Transplantation. 2004. vol 77. p1181-5.  
LOE 4, Fair, supports. 8 patients, observational, no control. Followed for 24 hrs. |
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Level</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Summary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LOE4, Fair, supports. Observational 10 healthy pts. Effects of Atropine |
LOE4, fair, supports. Observational 37pt, 5 with bradycardia. Inhospital TCP |
LOE5, Fair, supports. Randomized, open label. 2 groups, 60 pts each (post cardiac pts). Milrinone vs Dobutamine |
LOE 4, poor, supportive. case study 3 patients with inferior MI. with atropine resistant bradycardia.  
The author reported that three patients with acute inferior myocardial infarction with first degree heart block treated with aspirin (150mg) and streptokinase (1.5MU over 60 min), who developed atropine-resistant bradyarrhythmias (2 patients with complete heart block, one patient without) during or immediately following streptokinase. The bradyarrhythmias responded to aminophylline, thus avoiding the need for temporary pacing. |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>transcutaneous cardiac pacing for symptomatic bradycardia. Pacing Clin</td>
</tr>
<tr>
<td></td>
<td>LOE2, fair, indeterminate. 51 bradycardic patients, 27 paced</td>
</tr>
<tr>
<td>Kovarik 2008</td>
<td>Kovarik, J.M., et al., <em>A mechanistic study to assess whether isoproterenol</em></td>
</tr>
<tr>
<td>(isoproterenol)</td>
<td><em>can reverse the negative chronotropic effect of fingolimod.</em> J Clin</td>
</tr>
<tr>
<td></td>
<td>LOE1, fair , supports. 14 patients. randomized cross over study. Isoproterenol</td>
</tr>
<tr>
<td>Kovarik 2008</td>
<td>Kovarik jm, et al. <em>The ability of atropine to prevent and reverse the</em></td>
</tr>
<tr>
<td>(atropine)</td>
<td><em>negative chronotropic effect of fingolimod in healthy subjects.</em> Br J</td>
</tr>
<tr>
<td></td>
<td>LOE1, good, supports. RCT , placebo controlled, 2 period crossover. 24 pts.. Atropine</td>
</tr>
<tr>
<td>Kragie, 1992</td>
<td>Kragie, L. and B. Sekovski, <em>Theophylline--an alternative therapy for</em></td>
</tr>
<tr>
<td></td>
<td>LOE 4, fair, supports. Observational, no control. 11 pts. with 14 cases.</td>
</tr>
<tr>
<td></td>
<td>LOE 4. poor. supports. case report 3 pts. beta blocker overdose. Glucagon</td>
</tr>
<tr>
<td>Study</td>
<td>Reference</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>Study</td>
<td>Reference</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Description</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td>LOE4, fair, supports. Retrospective review 131 pts, unstable bradycardia. Atropine.</td>
</tr>
<tr>
<td></td>
<td>LOE4, good, supports. Observational 56 pts. Bradycardia. Inhospital TCP</td>
</tr>
<tr>
<td></td>
<td>LOE4, good, supports. Observational study 134 pts. Inhospital TCP</td>
</tr>
</tbody>
</table>
CITATIONS:

Final consensus bibliography

All articles bibliography